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THE MENTAL SYMPTOMS OF PELLAGRA.

THEIR RELIEF WITH NICOTINIC ACID.*†

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MENTAL changes as a part of the pellagra syndrome have been recognized by many physicians, and in areas where the disease is endemic these symptoms are so common and so striking that they have become associated with pellagra even by the lay observer. Various abnormal psychic states have been described in medical literature on pellagra, and some writers have thought that one or another psychosis was typical of this disease.

Subclinical pellagrins are noted for the multiplicity of their complaints, among which are many that are usually classified as neurasthenic. The most common of these symptoms are fatigue, insomnia, anorexia, vertigo, burning sensations in various parts of the body, numbness, palpitation, nervousness, a feeling of unrest and anxiety, headache, forgetfulness, apprehension and distractibility. The conduct of the pellagrin may be normal; but he feels incapable of mental or physical effort, even though he may be ambulatory.

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The noticeable and more serious mental signs of pellagra manifest themselves in various types of psychoses. The most common is perhaps that in which loss of memory, disorientation, confusion and confabulation are predominant. There are also types in which excitement, mania, depression and delirium may occur. In our experience, a paranoid condition is common in pellagrins. These patients, acting on their paranoid delusions, are more active than are other pellagrins with psychoses. We claim no priority in observing the difference in the mental symptoms in various patients, for many writers on the subject have attempted to classify the neuroses and psychoses of the disease. Niles[9] and Wood[20] noted the paranoid trend in pellagrins suffering from psychiatric difficulties. They recorded particularly the pellagrin's fear of and antipathy toward relatives, with delusions of persecution. There is not space for an involved discussion of the classification of the mental signs of pellagra. The case reports which follow may satisfy those interested in the classification of psychoses. Numerous definitions have been fitted to the term "neurosis," and it has been used in the past in many of the writings on pellagra. Although objections will probably arise to the use of this term, it will be used (for want of a better one) in the present report to describe the prodromal complaints listed above. In a language which is not noted for its preciseness, it will do for the purpose at hand. The same symptoms, of course, occur in association with many other diseases, but in the present study they will be considered as the prodromal part of the pellagra syndrome. The treatment described below is not advocated for any mental disability except for that associated with pellagra.

In September, 1937, Elvehjem, Madden, Strong and Woolley[1] reported that nicotinic acid cures blacktongue in dogs, a canine disease which is believed to be analogous to pellagra in human beings.[3,7,8,13,19,21] Since all food substances which have been found to be curative and preventive for canine blacktongue have likewise proved beneficial in the treatment and prevention of human pellagra, several investigators were encouraged to determine the effect of nicotinic acid on this disease. Spies, Cooper and Blankenhorn[16] have shown that pellagrins respond dramatically to the administration of this drug. Beneficial results have also been observed independently by other investigators in the field.[2,5,6,10,11b,18] Spies, Sasaki and Gross[17] and Spies, Bean and Stone[14] have mentioned briefly that the early and late mental symptoms of pellagrins in relapse and of subclinical pellagrins are relieved by nicotinic acid. In a larger series of cases it has been possible to institute control measures in order to study more specifically the mental symptoms of pellagrins in relapse and their response to nicotinic acid. Related studies on subclinical and mild cases have also been made. It is our purpose in the present paper to record some specific observations on the

treatment of the psychoses and "neuroses" of pellagra with nicotinic acid and the diethyl amide of nicotinic acid.*

Material and Methods. The present study includes the following groups: 60 pellagrins with acute psychoses and other manifestations of pellagra as shown in the table; 15 other pellagrins with no mental symptoms but with characteristic dermatitis, glossitis, stomatitis and gastro-intestinal involvement; 424 subclinical and mild pellagrins who have been subject to one or two annual recurrences of the disease; 26 patients with psychoses of other types; and 129 pellagrins who had had one or two recurrences of their "neurotic" symptoms each "pellagra season" since the onset of their disease.

A. *Pellagrins With Acute Psychoses.* A total of 60 pellagrins with acute psychoses was studied at the Hillman Hospital, Birmingham, and at the General Hospital, Cincinnati. All of these patients had typical pellagra and were admitted to these hospitals between September 15, 1937, and June 1, 1938. A summary of some of the more common symptoms and physical signs is given below:

TABLE 1.—SUMMARY OF 60 CASES WITH ACUTE PSYCHOSES.

Male, 19; female, 41. White, 29; colored, 31.

Symptomatology.

Mental symptoms	60	Porphyrinuria† (of 40 tested)	40
Weight loss	60	Diarrhea	33
Stomatitis	56	Tachycardia	32
Glossitis	56	Peripheral neuritis	21
Dermatitis	55	Vomiting	19

Type of Pellagra.

Endemic, 35. "Alcoholic," 6.
Secondary to organic disease, such as gastro-intestinal diseases, 19.

Method of Control.

Water and glucose by mouth	21
Only water by mouth	20
Diet low in antipellagric factor	10
Hospital diet	9

* The nicotinic acid used in treating the pellagrins with spontaneous and induced psychosis was supplied by Abbott Laboratories, Harris Laboratories, Merck & Co., and the S. M. A. Corporation. The S. M. A. Corporation furnished the nicotinic acid used in the subclinical and mild cases. The nicotinic acid used for nutritional studies in children was supplied by Mead Johnson & Co. Coramine, the diethyl amide of nicotinic acid, was supplied by Ciba Pharmaceutical Products. The vitamin B_1 used in the study was furnished through the courtesy of Merck & Co.

† The majority of pellagrins in relapse excrete in the urine increased amounts of an ether-soluble substance, or substances, which gives the color of porphyrin in 25% HCl.[17] The prompt disappearance of this substance from the urine following the administration of large amounts of nicotinic acid can be used as an early objective test. From our observations of some 600 patients, we have noted that the incidence of strongly positive tests was much greater during February and March than during May and June. We have observed, however, that the severity of the other manifestations of pellagra does not parallel the excretion of these ether-soluble substances in the urine. Dr. C. J. Watson, in a personal communication, has suggested that the color of this test may be due, at least in part, to mesobiliviolin, and has supplied us with pure mesobiliviolin which certainly gives a similar color. Further studies on this point are being made. It is interesting that the urine from dogs with spontaneous blacktongue does not give positive tests.

When one of this group entered the hospital, he was placed under the observation of one of the authors.* The method of study may be described as follows: A note was made of the mental symptoms and their apparent duration before entry and of their progress over a period of several days while the patient was in the hospital, maintained on a restricted diet and given no therapy. If no improvement in the mental symptoms occurred under these conditions, they served as an index for testing the potency of the therapeutic agent. A specific therapeutic agent is of value if the mental symptoms clear promptly in all cases when sufficient amounts of the substance are added as a supplement to the control diet, all other conditions remaining constant.

The 60 psychotic pellagrins were divided into four groups. Each pellagrin was observed during a control period which varied from 1 to 10 days. The first group was composed of 21 pellagrins who received from 100 to 200 gm. of glucose per day and drank water *ad lib.* during the control period; the second group was composed of 20 pellagrins who drank water but ate no food during the test period; the third group consisted of 10 pellagrins who were given only a basic diet[4] and water *ad lib.* for from 2 to 3 days; the fourth group consisted of the remaining 9 pellagrins who were offered an ordinary hospital diet and water *ad lib.* (these patients refused to eat more than small amounts of food and their symptoms became worse). At the end of the control period, nicotinic acid, 500 to 1000 mg. daily, was administered orally to 49 of the patients. A total of 100 mg. daily, in 5 doses of 20 mg. each, was given intravenously or intramuscularly in 3 cases. Coramine ($C_{10}H_{14}OH_2$), the diethylamide of nicotinic acid, was administered orally in doses of 2 to 5 cc. daily to 8 of the 60 patients, until a total of from 20 to 50 cc. had been given. After improvement occurred every patient was placed on a well-balanced, high vitamin diet.

Observations. *The Curative Effect of Nicotinic Acid and Coramine on the Acute Mental Symptoms of Pellagra.* The severe psychoses of pellagra in the 60 patients who developed the psychosis spontaneously were relieved following the administration of coramine or nicotinic acid. Within 10 hours to 6 days after medication was begun, all of the patients had improved. So long as the patients were kept on a maintenance dose of nicotinic acid, no recurrence of symptoms was noted during the subsequent 2 to 4 months' period of observation. Similar studies with coramine are now being made.

The progress of a psychotic pellagrin under treatment with

* We were given invaluable assistance by the professional and administrative staffs of both hospitals, and are particularly indebted to Dr. J. B. McLester and Dr. Robert E. Stone; Miss Jean Grant, dietitian; Miss Ann Van Blaricom, Mrs. Verna Moore, and Miss Willadine Robbins, nurses; Miss Elisabeth Zschiesche, Miss Nelwyn Huff, and Miss Helen Grant, technicians; and Dr. Yasuo Sasaki, E. S. Gross, and S. P. Vilter, chemists.

nicotinic acid or coramine is probably best illustrated by the representative case report which follows:

CASE 1.—M. T. (No. 121169), a 55-year-old married negress, was brought to the Hillman Hospital on April 7, 1938, with hallucinations, delusions, dermatitis, diarrhea and stomatitis.

Medical history, family history and *past history* were not contributory.

Present Illness. The onset of the present illness was indefinite. For years the patient's diet had consisted chiefly of cornbread, black-eyed peas, fat meat, potatoes and greens. During the 2 to 3 weeks before admission, she had become progressively worse, developing anorexia; abdominal burning and discomfort ("like something eating my insides out"); nausea; diarrhea (20 to 25 stools per day), associated with tenesmus; burning and soreness of the mouth, tongue, and throat; increased salivation; burning and breaking out of the skin of the face, upper extremities and perineum; pain and tenderness of the genitalia associated with vaginal discharge; insomnia; nervousness; "foolishness and craziness in the head;" vertigo; loss of weight; and general weakness. During the week prior to admission to the hospital she had eaten little or no food because her mouth was too sore. The use of alcoholic beverages was denied.

Physical Examination. Physical examination, upon admission, revealed a well-developed, undernourished negress picking at the bedclothes, tossing about in bed, and requiring restraints.

Skin: Characteristic pellagrous dermatitis covered the greater portion of the ears, nose, face, malar prominences, forehead and lids of the eyes. In places these lesions were surrounded by a zone of erythema and slight tenderness. Pellagrous lesions also extended over the dorsa of the hands and upward around the wrists and over the ventromedial aspect of the arms. The affected skin appeared devitalized, darkly pigmented and was covered with many large blebs. The skin was broken over several of the joints. A similar pellagrous lesion, from 6 to 8 inches in diameter, was present in the suprasternal notch. The upper borders of this lesion extended to encircle the neck, thus forming a typical "collar of Casal." The skin of the legs was dry and rough. Areas around the hair follicles were deeply pigmented. The perineum presented a wide area of excoriation which was moist and covered with foul-smelling débris.

Mucous Membranes: Nose: The mucosa was fiery red, slightly swollen and partially covered with crusts.

Mouth: The lips were swollen and covered with crusts. The mucosa of the mouth and of the tongue, fauces and oral pharynx was reddened, slightly swollen, tender and presented many ulcers of varying size, the surfaces of which were covered with gray exudates. The tongue which was thick, reddened and tender had large ulcers on the ventrolateral surfaces. There was a striking increase in the flow of saliva (200 cc. per hour).

Vulva and Vagina: The former was swollen and tender. The mucosa of the vagina was fiery red, swollen, tender and contained several small ulcers.

Neuropsychiatric Examination. Upon admission the patient was apprehensive, disoriented and refused to talk in detail about the "foolishness and craziness in the head." She responded to questions and commands slowly or not at all. She had visual and auditory hallucinations which centered particularly around religious subjects and persons who wished to kill her, or animals and creatures which annoyed her. No impairment of memory was detected at the time of admission to the hospital, but she would not coöperate for mental testing. The motor and sensory systems were normal, with the exception of slight hypesthesia and hypalgesia of the distal portions of the upper extremities. This became progressively less in an ascending

manner, and the border where sensation became normal was not well defined. The tendon reflexes were very active; the plantar responses were flexor in type.

Laboratory Findings. Red blood cells, 3,800,000; hemoglobin, 67%; leukocytes, 7700 (neutrophils, 62%; lymphocytes, 38%). Blood Wassermann positive; spinal fluid Wassermann negative. The urine contained a trace of albumin, but otherwise was not abnormal, except for increased quantities of ether-soluble coproporphyrin (or some substance resembling it in ether solubility and color appearance in 25% HCl) before treatment.

Medication and Diet. During the first 96 hours of hospitalization, the patient was given daily 20 cc. of coramine orally, in 5 doses of 4 cc. each. During the first 36 hours she received, in addition to the coramine, only 10% glucose and water by mouth. Thereafter, as she became free from nervous and digestive symptoms she was given the regular hospital diet with the intermediate feedings of milk-egg mixture, as she desired, until discharge.

Progress. Within 12 to 16 hours after treatment was instituted, the ptyalism had decreased and the mucosa of the mouth, tongue, nose and vagina appeared less swollen, red and tender. At the end of 24 hours, the fiery redness was replaced by a bluish-gray cast, and the salivary excretion was normal in amount. She asked for food and stated that this was the first time since the onset of her illness that she had been hungry.

After 48 hours, she became quiet and coöperative and had insight into her mental condition which we learned had been very distressing to her during the week prior to admission. This fact had not been fully appreciated at the time of the initial examination, partly because of her apprehensiveness, maniacal outbursts, and her hesitancy to discuss her symptoms. She stated that her head began to clear 24 to 36 hours after treatment, and that now she knew that the "craziness and foolishness in the head" was unreal. The following account of the symptoms present before admission was obtained at this time: She thought she was being poisoned and otherwise abused by her neighbors. She saw and heard monkeys, rats and cows running around her, and felt bugs, snakes and worms crawling on her. She had dizziness, blurring of vision and was "unable to remember things." She could not direct her attention toward her usual household duties, "because I couldn't keep my mind on it."

Improvement continued steadily: 36 hours after treatment had been instituted and while she was still on the glucose restricted diet, the mucosa of the mouth appeared normal, except at sites of deep ulceration; the vaginal mucosa had healed; the redness and swelling had subsided; and the skin showed signs of healing. At this time she took an adequate diet eagerly and within a week all pellagrous lesions had healed.

Temperature and heart rate: During the first 60 hours the temperature varied between 98.6° and 100° F., and the heart rate between 80 and 90.

She was discharged mentally clear and in good physical condition 9 days after admission.

Comment. It was learned from the histories obtained from the family and friends of the 60 patients of this group that psychotic behavior had been present from 1 to 83 days. Most of these patients had had some sign of psychosis from 1 to 2 weeks. After treatment was begun, recovery occurred in from 10 hours to 6 days.

It is to be understood that no pellagrin with a chronic psychosis of years' duration, of the type often found in custodial mental hospitals, was treated. We believe that the patients treated in this series, because of their severe mental symptoms, would have been

committed and thus might have become chronic types. The mental symptoms of these 60 pellagrins were of the severe acute type. Many of the patients were violent and severely hallucinated; others were severely depressed. It is difficult to describe the change in these patients after therapy was begun. The maniacal patients became calm; the depressed, cheerful; and, legally speaking, the insane again became sane. After recovery these patients often had an excellent memory of their actions, ideas, and of their surroundings during the psychotic period. They were usually completely adjusted after treatment, except for some perplexity about the cause of their actions during the psychosis. "What made me act that way?" and "Was I crazy?" are questions that are frequently asked at this time. In most cases improvement was abrupt, occurring sometimes overnight.

We have not observed a case of acute pellagra that has not responded promptly to nicotinic acid therapy, whereas our previous experience, as well as that of others, would indicate that these cases were likely to die if treated by ordinary methods and were almost certain to die if they went untreated.

Thirty cases, after relief from the acute psychoses of pellagra, have been kept free from mental signs by the continued use of nicotinic acid and without change in their previous environment. Recurrences of mental symptoms of similar severity in other patients have also been prevented[11] by the daily ingestion of large amounts of dried brewers' yeast (Harris Laboratories, Anheuser-Busch, Mead Johnson & Co).

Twenty other psychotic pellagrins with mental symptoms failed to maintain recovery induced by nicotinic acid when it was discontinued and the patient returned to his old environment. In our studies 2 years ago,[15] we were able, by extraordinary effort on the part of the physicians and a large nursing staff, to feed the patients large quantities of a well-balanced diet and large amounts of dried brewers' yeast, in some instances supplemented by injections of liver extract. This treatment, when directed individually, was effective; but the convalescence was slow and the attention required for each patient is prohibitive on an ordinary ward of a general hospital. In contrast to the method applied in the above studies, the great majority of pellagrins do not have such individual attention. As a result, the mortality rate is high, and a considerable number of the patients who do improve make only a partial recovery and are subsequently sent to a hospital for the insane. This suggests that some systematic check should be made for cases of this nature in the large mental hospitals. Such studies are now under way.

The remaining 10 patients did not report for subsequent observation.

B. *Pellagrins With Extensive Mucous Membrane and Dermal Lesions and Severe Gastro-intestinal Involvement, but No Mental Symptoms.* An alternate method of study which we used was a comparative observation of the course of the disease in 15 pellagrins who had no mental symptoms but did have extensive skin and mucous membrane lesions and involvement of the gastro-intestinal tract. These patients, who were too ill to ingest an ordinary diet, were given 10% glucose solution. Certain of them developed psychoses while restricted to such a diet. If a medicament has therapeutic value under these circumstances, the acute mental signs which develop under controlled conditions should remit promptly if sufficient amounts of the substance are added to a glucose diet, all other factors remaining constant.

Observations. Within the 10-day period of observation, 10 patients in this group developed a psychosis and 5 did not. To 5 of the 10 cases who developed a psychosis, 500 mg. of nicotinic acid were administered daily in 10 50-mg. doses. This was the only supplement to the glucose diet. Prompt relief of the symptoms occurred in all cases. Before they were discharged from the hospital, all of the patients were given a high caloric, high vitamin diet in addition to nicotinic acid. No recurrence of symptoms was noted during the subsequent 2 to 4 months' period of observation.

A representative case report of a patient whose psychosis occurred on a glucose-restricted diet and who was cured promptly by the addition of nicotinic acid to the glucose, is given below.

Case 2.—E. T. (No. 121883), a 31-year-old negro widow, was admitted to the medical service of the Hillman Hospital on May 10, 1938, complaining of weakness and diarrhea of about 5½ months' duration.

Family history and *past history* were irrelevant.

Present Illness. The onset of the present illness was insidious and occurred about 5½ months before admission, with the development of progressive general weakness; intermittent diarrhea; vaguely described general abdominal discomfort; loss of weight; and a bloody vaginal discharge. Six weeks before admission she was examined in the gynecologic and proctologic clinics, where the following diagnoses were made: Uterine fibroids, rectal stricture, mucous colitis and secondary anemia. Palliative therapy afforded only temporary relief and all of the above symptoms persisted and gradually became worse. During the 7 to 10 days before admission, signs of dermatitis (increased pigmentation, roughness, induration and slight tenderness) were present over the hands, forearms and elbows. She developed anorexia; soreness and burning of the mouth; increased salivary flow; burning discomfort in the epigastric and substernal region; nausea; increased weakness; nervousness; and, at times, vertigo. There was no emesis, personality change or symptoms of peripheral neuritis.

Physical Examination. The physical examination revealed a poorly nourished negress who appeared to be chronically ill. Temperature, 98° F., pulse 75, respiration 21, blood pressure 120/80.

The skin was dry, loose, rough and deeply pigmented, particularly over the bony prominences. Large, well-demarcated areas of pellagrous dermatitis were present over the dorsa of the hands, wrists, forearms, elbows and over the external genitalia, extending around the anus and down the

medial aspect of the thighs. There was a slight diffuse lesion of the buccal and lingual mucosa, characterized by swelling, redness, tenderness and increased salivary flow, but no ulceration. The vaginal mucosa was diffusely and moderately red and tender, and there was vaginal discharge. The vulva was swollen and tender, and presented several minute ulcers at the mucocutaneous junction. A grayish-white exudate surrounded the anus. Digital examination was not done because of extreme tenderness. The examination otherwise was not remarkable except for an enlarged, firm uterus.

Neuropsychiatric Examination. Reflexes were normal. The motor and sensory systems were normal. At times, the patient complained of nervousness and vertigo. No other positive psychiatric findings were detected.

Laboratory Findings. Red blood cells, 2,500,000; hemoglobin, 45%; white blood cells, 6600 (neutrophils, 87%; lymphocytes, 13%). Blood Wassermann negative. The urine was not remarkable except that it was positive for an ether-soluble substance, or substances, giving the color of porphyrin in 25% HCl.

Course. During the first 6 days in the hospital she was offered the regular hospital diet, but because of oral pain, refused to eat. She received paregoric and bismuth for the diarrhea. Her general condition slowly became worse. She was given only water and 2000 cc. of a 10% solution of glucose by mouth daily for the next 7 days. No other food or medication was given. During this period she became worse. She complained more than previously of the soreness of her mouth, tongue and vulva; dizziness; nervousness; insomnia; and burning of the feet. Examination of the mucosa at that time showed it to be ulcerated, more tender, and of a deeper red color. She developed severe vomiting and diarrhea, the ptyalism increased and she became restless and appeared to be uncomfortable. Her illness continued to progress rapidly. Seven days after she had been subsisting on this diet of only glucose and water, the following progress note was made: "The mucosa of the mouth and tongue is fiery red and tender, and several large ulcers are now present over the buccal mucosa, fauces and pharynx; salivation has increased to 1500 cc. per day; the skin of the extremities is about the same as before, but that of the perineum is moist and partially excoriated. Her mental condition is now abnormal. She is disoriented as to time, reacts sluggishly, and is unable to recall recent events. She has visual and auditory hallucinations. She has developed insomnia and obviously is restless and confused." Her condition had become critical.

Nicotinic acid was begun at this time. During the next 48 hours she was given glucose and a total of 2000 mg. of nicotinic acid, in divided doses of 50 mg. each, by mouth. Before the 48-hour period of therapy was over, she had become quiet, seemed clearer mentally and slept without difficulty. She complained less of the soreness and tenderness of her mouth and tongue; the intense redness of the tongue had decreased remarkably, and the ptyalism had decreased to 200 cc. per day. At this time the administration of nicotinic acid was discontinued and glucose was given as before. During the 48 to 72 hours after the treatment with nicotinic acid was discontinued, there was slight improvement of the condition of the mucosa. Her mental condition, however, became worse, and she was maniacal, anxious and confused, and again had visual and auditory hallucinations.

Nicotinic acid therapy was resumed, and a total amount of 1700 mg. of this substance was administered during the first 48 hours when improvement again took place. Thereafter, a total daily dose of 1000 mg. was given for a period of 1 week, during which time the patient also received a high caloric, high vitamin diet. The mucous membranes healed rapidly, the mental symptoms cleared completely, and within a week there was

considerable desquamation of devitalized skin. Her appetite, strength and general condition likewise were improved remarkably.

During both relapses there was an elevation in temperature from 98° to 100° F., and an increase in pulse from an average of 80 up to 95. The temperature and pulse rate returned to normal during the final week of hospitalization.

C. *Subclinical and Mild Pellagrins.* In the pellagra clinic at the Hillman Hospital, the pellagra-preventive effect of nicotinic acid has been studied in 199 patients who have had recurrences of pellagra each spring over a period of several years. The majority of these pellagrins have had one or more recurrences of some of the mental symptoms of pellagra each pellagra season since the onset of their disease. The patients reported weekly for examination, and at the time of each visit a record was made of their weight, physical condition and of any untoward sensations or changes in sensations of which they complained. They were also questioned carefully regarding any change in dietary habits and environment. All have been kept free from recurrences of their mental symptoms from February 15 to July 1, 1938, by the use of nicotinic acid administered in daily doses of 100 to 600 mg. No change worth noting has occurred in their environment or dietary habits.

It is noteworthy that many physicians who wrote on pellagra before the publication of Goldberger's work contended that pellagra should be classified in the group of neuroses. Every pellagrin has one or more symptoms which might be considered those of a neurosis. It is because of the multiplicity of these vague, subjective manifestations of which the pellagrin complains that one must be extremely wary in interpreting the state of bodily function and especially in evaluating neuropsychiatric disorders. The selection of patients has been most arbitrary and has in great part depended upon a knowledge gathered from previous studies of these patients. Particular stress was laid on choosing patients who, after previous periods of treatment, had no vague, indefinite complaints, thus eliminating those persons who had chronic complaints. We have attempted to observe specifically the relief of such prodromal symptoms of pellagra as fatigue, insomnia, anorexia, vertigo, paresthesias, palpitation, nervousness, headache, forgetfulness, apprehension and distractibility. This is manifestly a task fraught with danger. To mention one pitfall, the mere attendance at a "pellagra clinic" whose work has been favorably bruited about by word of mouth and otherwise, conceivably might be responsible for the relief of many symptoms. It was in an attempt to avoid suggestion that the following method was used in studying the effect of nicotinic acid on on the "neuroses" of mild pellagra.

There were 225 patients in the pellagra clinic who did not come under observation early enough during the spring of 1938 to receive nicotinic acid as a preventive measure. At the time of examination

these patients had developed mild pellagra and some of the above symptoms. They were arbitrarily given one of four medicaments, all of which were similar in appearance: 75 received acetylsalicylic acid; 50 received sodium bicarbonate; and 100 were given vitamin B_1.

Observations. Following the administration of nicotinic acid to subclinical pellagrins with prodromal symptoms and to mild pellagrins with the same type of symptoms, there is prompt relief.* During the spring and summer seasons of 1938 the great majority of these patients has remained free from a return of these prodromal symptoms, as long as adequate amounts of nicotinic acid were administered frequently. In a number of instances, however, the symptoms were returning and we found it necessary to increase the daily dosage of nicotinic acid. In some cases, we have had to give as much as 600 mg. per day, in order to keep these persons free from such symptoms. The patients receiving the other three medicaments reported little or no change in symptoms. Some described relief during the first few days, after which time they stated that the medicine did not help. Without their knowledge the medication of all of the patients in this group was later changed to nicotinic acid. In each case, following the administration of nicotinic acid, there was prompt relief of the majority of the neurotic symptoms. On nicotinic acid therapy the ambulatory pellagrin regained energy and appetite and many resumed work. This striking relief occurred within 1 to 12 days following the administration of 5 or 6 doses of 100 mg. each per day (often a smaller dose was effective). This improvement has been almost universal in this group of cases. We do not claim, however, that the administration of nicotinic acid will be followed by complete relief of the same symptoms if unassociated with pellagra.

Probably of greater significance than the relief of "neurotic" symptoms following the administration of nicotinic acid is the return of these symptoms when, without the patient's knowledge, nicotinic acid is withdrawn and another medicament of similar appearance is substituted for it. When nicotinic acid was withdrawn suddenly during a period when the patient was obtaining benefit from it, the original subjective manifestations usually returned within a week.

Spies and Aring[12] have reported that vitamin B_1 is beneficial in treating the manifestations of peripheral neuritis associated with pellagra, but that it does not cure the alimentary and central nervous system disturbances of pellagra. Studies on a large number

* Preliminary studies on 75 children with characteristic pellagra have shown that the majority of them have dizziness, irritability, stomach upsets, flight of ideas, and inability to get along well in school or with other members of their family. These symptoms usually disappeared promptly following the ingestion of tablets of nicotinic acid.

of mild pellagrins who were given vitamin B_1 have shown that the mental symptoms grow progressively more severe on vitamin B_1 therapy, but respond promptly following the administration of nicotinic acid. This investigation is being continued, but the following 2 cases illustrate this point:

Case 3.—L. M. F. (Clinic case), a 27-year-old white female, was first seen in the clinic of the Hillman Hospital on May 14, 1938, chiefly because of pain and burning of the feet and legs of about 2½ months' duration.

Family History. Two members of her family have had pellagra.

Past History. This patient had "pellagra," or an illness similar to the present illness, in the spring of 1934 and since that time has had 2 recurrences of the disease each year, in the spring and late summer.

Present Illness. The onset of the present illness was insidious. About 2½ months before admission the patient developed itching and burning of the skin of the upper extremities and, to a less extent, of the face, neck and shoulder girdle. Later these areas became intensely red and deeply pigmented. As the disease progressed the patient developed soreness and burning of the tongue and mouth; anorexia; ptyalism; constipation; general weakness; loss of weight; nervousness; increased irritability; vertigo; impairment of memory; insomnia; "foolish dreams;" and burning and pain in the feet and legs. These symptoms slowly became worse. During the week prior to the patient's first visit to the clinic, the pain in her feet and legs became considerably worse and was associated with swelling and numbness.

Her usual weight was about 117 pounds; at the time of admission it was 104 pounds. There was no evidence of pellagra when the patient was first seen in the clinic, but she had peripheral polyneuritis, most marked in the lower extremities.

Her diet had consisted chiefly of carbohydrates but also included small amounts of green vegetables. She ate very little lean meat, eggs or milk.

Course. No therapy was prescribed when the patient first visited the clinic on May 14. Four days later consultants concurred in the diagnosis of peripheral neuritis, and she began taking vitamin B_1 in amounts of 10 mg. daily (tablet form). Ten days later she returned to the clinic and reported considerable relief from anorexia and from the burning in her feet, but she complained of generalized aching. At that time the dosage of vitamin B_1 was increased to 40 mg. daily. She was confused, and said that she worried too much and could not concentrate. Three days later she had no discomfort in her feet but she complained at that time of diarrhea (up to 9 stools per day), abdominal cramps, nausea, emesis several times, slight soreness of the mouth and tongue, and increasing weakness of 3 days' duration. Nicotinic acid, 300 mg. daily, was prescribed along with the vitamin B_1. Within a few days the soreness of her mouth and tongue and the "slobbering" (ptyalism) disappeared, and within a week the diarrhea and abdominal discomfort had subsided. Her appetite, strength, nervousness and vertigo also improved progressively. She said that she had not felt better in months. Before treatment with nicotinic acid the urine repeatedly contained ether-soluble substances giving the color of porphyrin in 25% HCl. The urine, 48 hours after treatment with nicotinic acid, was negative for such substances.

Case 4.—E. B. (Clinic case), a 35-year-old white married woman, came to the clinic for the first time on May 18, 1938, because of pain and burning of the feet and legs, accompanied by characteristic pellagrous dermatitis and glossitis.

Family history was irrelevant.

Past History. She had pellagra for the first time during the spring of 1936 and had a recurrence the following spring. The symptoms of these illnesses were similar to those of the present illness.

Present Illness. The onset was insidious. About 2½ months before her first visit she developed dermatitis of the hands, arms, feet and legs; soreness and burning of the mouth and tongue; ptyalism; general abdominal discomfort; nausea; vertigo; emesis on occasion; anorexia; diarrhea; headache; nervousness; insomnia; impairment of memory; sharp, shooting and aching pains; burning and slight swelling of the feet and legs; loss of weight; general weakness; cardiac palpitation and exertion; vaginal discharge; and itching and burning of external genitalia. These symptoms varied considerably in severity from time to time, and her general condition steadily became worse. There was excruciating tenderness to pressure in the extremities. The patient had mild pellagra and peripheral neuritis as evidenced by tenderness of the nerve trunks and loss of tendon reflexes in the legs.

Course. During the first 4 days she was given 10 mg. of vitamin B_1 daily by mouth and, thereafter, 20 mg. per day. During the first 10 days of vitamin B_1 therapy her appetite improved and the burning, pain and swelling of her feet and legs subsided completely. However, during the following week she became remarkably worse, her husband reporting that she had been "crazy" and did not know what she was doing. She was extremely dizzy; unsteady on her feet (had to be assisted in walking); talked incoherently; had visual and auditory hallucinations; was disoriented as to time, place and person; and complained of being "numb all over." At this time, 10 days after first coming to the clinic, she was given, in addition to the vitamin B_1, 500 mg. of nicotinic acid daily.

During the following 12-day period there was progressive improvement in her general condition. She said she felt "a lot better," did not appear confused, "knew what she was doing," her appetite was better and the aching had disappeared. Her husband stated that she was now mentally well. Her diet and environment remained the same throughout the study, except that the patient refused to eat much of what was offered to her until vitamin B_1 therapy was instituted.

Laboratory Findings. Red blood cells, 3,250,000; hemoglobin, 63%. As in the preceding cases, the urine on repeated examination contained an ether-soluble substance giving the color of porphyrin in 25% HCl, which disappeared following treatment with nicotinic acid.

Comment. The manifestations of peripheral neuritis of pellagra improved promptly following the administration of large amounts of vitamin B_1. The present study, which is being continued and which will be reported in detail later, shows that vitamin B_1 does not cure the mucous membrane lesions or the mental symptoms of pellagra, but that it does aid in curing the peripheral neuritis.

D. *Patients With Psychoses Not Associated With Pellagra.* The effect of nicotinic acid on the mental symptoms of pellagra led to the thought that this substance might be efficacious in the treatment of other psychoses. This might be expected to be the case, especially in psychoses alleged by some to be related to deficiency states other than pellagra; for example, alcoholic hallucinosis, delirium tremens, and Korsakow's psychosis. Accordingly, we administered nicotinic acid to twenty-six patients suffering from the following mental diseases: alcoholic hallucinosis, Korsakow's psy-

chosis (following chronic alcoholism), manic depressive psychosis (depressed phase), involutional psychosis, psychosis with cerebral arteriosclerosis, and schizophrenia. The amount of nicotinic acid was rather large (1 to 2 gm. daily in divided doses); it was given as a supplement to a regular house diet and the period of treatment was as long as 50 days in some cases. This treatment was without psychiatric results in these cases. However, it caused flushing and a feeling of warmth in the skin, as described in detail recently by Spies, Bean and Stone.[14] It is our impression, therefore, that the psychoses are benefited only if they are a part of the syndrome of pellagra.

Summary and Conclusions. 1. The present studies suggest that nicotinic acid in adequate amounts is a specific therapeutic agent for the acute mental symptoms of pellagra. Both spontaneous and induced psychoses of pellagra respond promptly following this therapy. Coramine, the diethyl amide of nicotinic acid, also is beneficial in the treatment of the abnormal mental symptoms.

2. The psychoses present in 26 non-pellagrous persons did not improve following the ingestion of these drugs.

3. The so-called "prodromal" or "neurotic" symptoms of pellagra usually disappear following the administration of nicotinic acid. These studies were conducted in such a manner that suggestion was eliminated, and they indicate that the vague, subjective, prodromal symptoms are evidence of disordered function.

4. These studies show that frequently repeated large doses of nicotinic acid prevent the development of mental symptoms in subclinical pellagrins and in mild pellagrins.

5. The minimal dose of nicotinic acid has not been determined but seems to vary from case to case. It is tentatively recommended that each patient with severe mental symptoms receive a total of at least 500 mg. per day. It is preferable to give this in 10 doses. In the extremely severe cases convalescence seems to be shortened by the administration of 1000 mg. daily. Since nicotinic acid is only one of the essential chemical substances present in the well-balanced diet, we suggest that all patients with pellagra be given a well-balanced diet whenever possible, even though nicotinic acid is used as a supplement.

6. The methods which have been described appear to offer a lead in the study, under controlled conditions, of one type of mental disease before, during and after mental signs are in evidence.

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The diagnosis of borderline cases of acute alcoholism has always been difficult. Because of the close association of alcohol with trauma, crimes of violence, automobile accidents and the like, the medico-legal aspect of alcoholic intoxication has become of great importance. Testimony based upon clinical findings alone is insufficient proof in a majority of cases to most courts and juries. The ability to demonstrate the presence of alcohol in a given individual would be definitely desirable. Of still greater importance and significance would be the ability to determine whether a given amount of alcohol is sufficient to produce intoxication.

It was believed that a study correlating the clinical findings of acute alcoholism with the concentration of alcohol in the blood and urine in a large series of cases might give definite chemical standards for the diagnosis of the condition. Consequently, a total of 1159 patients admitted to this hospital with a pre-admission diagnosis of acute alcoholism have been studied with regard to this correlation over a 3-year period.

Others have performed like studies, the major part of the work coming from foreign authors. Hoffman,[5] reporting 642 cases, stated that intoxication occurred in 100% of all cases when the concentration of alcohol in the blood was 0.20 to 0.25% and above. Widmark[11] and Schwarz,[9] in 592 and 905 cases respectively, found intoxication in all cases in concentrations of 0.25 to 0.30% alcohol in the blood or over.

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Others have performed like studies, the major part of the work coming from foreign authors. Hoffman,[5] reporting 642 cases, stated that intoxication occurred in 100% of all cases when the concentration of alcohol in the blood was 0.20 to 0.25% and above. Widmark[11] and Schwarz,[9] in 592 and 905 cases respectively, found intoxication in all cases in concentrations of 0.25 to 0.30% alcohol in the blood or over.

Comparatively few data have been reported from this country. Bogen,[1] analyzing 250 cases in which alcohol was present in the urine, concluded that intoxication occurred in most cases in concentrations over 0.20% alcohol. The blood alcohol content of 200 intoxicated cases was reported by Johnson[7] but no evaluation of his results are possible because of the scarcity of data in the article. Turner[10] investigated 32 cases and believed that intoxication occurred in most cases when the concentration of alcohol in the blood varied from 0.20 to 0.30%. Harger,[3] in 140 cases, found 100% intoxication in alcoholic concentration in the blood of 0.20 to 0.25% or over.

Methods. The method of the determination of the alcohol content of the blood and urine as devised by Heise[4] in 1934 was used. It utilizes the reducing power of alcohol to decolorize potassium dichromate in acid solution.

On admission 5 cc. of blood were withdrawn from the median basilic vein and transferred to an oxalate bottle. Precautions were taken to have the arm wiped dry of alcohol used for sterilizing purposes before taking the sample. When possible a sample of urine was also obtained.

Blood. Two cc. of oxalated blood were placed in an 800-cc. Kjeldahl flask and about 15 cc. of a picric-tartrate reagent were added. (Picric-tartrate reagent—one-half saturated picric acid containing about 10% tartaric acid.) The resulting mixture was distilled and the first 10 cc. of the distillate collected. An aliquot portion, 2 cc. and fractions of this amount, were then added to separate tubes containing 1 cc. of potassium dichromate solution (N/15 $K_2Cr_2O_7$ in 50% H_2SO_4), the final volume being made up to 3 cc. in all tubes. They were then placed in a boiling water bath for 10 minutes and compared with standards containing known amounts of alcohol. Results were expressed in terms of percentage of alcohol by weight per 100 cc. of blood.

Specificity. While the method is not specific for ethyl alcohol, the blood distillate of non-alcoholics ordinarily contains no other reducing substances. Blood specimens taken from 44 patients on various wards of the hospital were negative for volatile reducing substances. Acetone bodies may interfere but may be detected and eliminated by qualitative tests. The highest reading in terms of alcohol percentage obtained from 7 patients with 4+ acetone was only 0.03% alcohol. Ether and paraldehyde have no reducing power. Blood taken from patients following full ether anesthesia and from 13 cases of paraldehyde poisoning exhibited no reducing properties with this method. Methyl alcohol will interfere but may also be detected by appropriate qualitative tests.

Urine. A mixture of 10 cc. of urine and 10 cc. of the picric-tartrate reagent was distilled and the first 10 cc. of the distillate was collected. One cc. and fractions of this amount were added to tubes containing 3 cc. of the dichromate solution, the final volume being made up to 4 cc. in all tubes. They were then placed in a boiling water bath for 4 minutes and compared to known standards. Results were expressed in terms of percentage of alcohol by weight per 100 cc. urine.

Specificity. The urine of individuals taking urotropine may exhibit volatile reducing properties providing formaldehyde has been produced in the kidneys. The highest reading in terms of alcohol concentration in a series of cases using urotropine in the usual dosage was 0.05% alcohol. Formaldehyde, therefore, should be eliminated as an interfering agent by

qualitative methods.* Acetone bodies are also volatile reducing substances but have never shown readings higher than 0.03% in terms of alcohol concentration. No other volatile reducing agents were detected in the urine of a group of over 200 non-alcoholics.

TABLE 1.—CLINICAL CRITERIA ESSENTIAL FOR DIAGNOSIS OF CLINICAL INTOXICATION.

I. Patient *must* have a gross gait abnormality or be unable to walk.
II. In addition to I, at least two of the following tests *must* be positive.
  1. Gross abnormality of speech or unable to speak.
  2. Flushed face.
  3. Dilated pupils.
  4. Alcoholic odor of breath.

Clinical Material. A. *Criteria for Diagnosis of Clinical Intoxication.* The following criteria were adopted for the clinical diagnosis of acute alcoholic intoxication. As shown in Table 1, gross gait abnormality must be present, and in addition at least two of the following tests must be positive: abnormality of speech, flushed face, dilated pupils and alcoholic odor of the breath. In the detection of gait abnormalities the individual was asked to walk from one side of the room to the other. If gross swaying, reeling or staggering were not present, the test was considered negative. For a detection of speech abnormality, the patient was required to answer simple questions only such as his name, residence, and so on. If definite slurring or incoherence was not present the test was considered to be negative. If the individual was comatose and was unable to walk or talk, final decision as to whether or not the defects were produced by alcohol was determined by subsequent ward observation.

B. *Analysis of the Cases.* A total of 1159 consecutive cases admitted with a pre-admission diagnosis of acute alcoholism were studied. In 1150 cases blood was obtained for analysis: 1000 cases were alcohol-positive and 150 alcohol-free. In 372 of the 1000 cases showing alcohol in the blood, the urine was also obtained for analysis. In 9 cases only the urine was obtained in all of which alcohol was present.

Of the 150 cases who were free of alcohol at admission, 78 were known chronic alcoholics. Table 2 shows the correct diagnosis in the other 72 cases. It is interesting to note the various conditions which may be confused with acute alcoholism particularly if the patient is comatose, which condition was present in 37 cases. Of these, 16 resulted from overdosage of either paraldehyde or barbital derivatives, while diabetes mellitus, uremia, cerebral injuries, cardiovascular accidents and schizophrenia accounted for nearly all others. The remaining 36 cases occurring in non-alcoholics were admitted in a non-comatose condition.

* One gram phloroglucinol is dissolved in 100 cc. of 10% NaOH; 0.1 cc. of this reagent added to 1 cc. of the distillate produced a red color in the presence of formaldehyde.

TABLE 2.—CORRECT DIAGNOSIS OF ALCOHOL-FREE CASES WITH PRE-ADMISSION DIAGNOSIS OF ACUTE ALCOHOLISM.

Correct diagnosis.	No. of cases.	No. of cases comatose.
Barbital poisoning	15	8
Paraldehyde poisoning	13	8
Cardiovascular accidents	11	5
Schizophrenia	7	2
Fractured skull	7	7
Psychosis	4	1
Epilepsy	3	1
Diabetes mellitus	2	2
Septicemia	2	0
Uremia	2	2
Anemia	2	0
Acute appendicitis	1	0
C.N.S. lues	1	1
Ruptured bladder	1	0
Ruptured gastric ulcer	1	0
Total	72	37

TABLE 3.—NUMBER AND PERCENTAGE OCCURRENCE OF DESIGNATED CLINICAL CRITERIA IN 1000 CASES WITH ALCOHOL IN THE BLOOD.

Clinical criterion.	No. of cases with positive clinical criterion.	Per cent positive clinical criterion.
Alcoholic odor	903	90.3
Abnormality gait or inability to walk	750	75.0
Abnormality speech or inability to talk	721	72.1
Dilated pupils	713	71.3
Flushed face	606	60.6

In Table 3 are tabulated the number of positive clinical tests with their percentage occurrence in the 1000 cases showing alcohol in the blood. It will be seen that an alcoholic odor was present in the greatest number of cases, namely 903 (90.3%). Gait and speech abnormalities were found in 750 and 721 cases respectively. In most instances, abnormality of speech accompanied an abnormality of gait. The incidence of dilated pupils closely followed, occurring in 713 cases, while that of flushed face was lowest with a total of 606 cases.

Using the criteria for acute clinical intoxication as outlined in Table 1, a diagnosis of the condition was made in 740 cases (74%). Of the 5 clinical criteria, examination of locomotion was most important since the diagnosis of clinical intoxication could not be made in its absence. There were only 10 instances in the entire group in which a gait abnormality was unassociated with less than 2 of the other clinical criteria, thus making a positive diagnosis impossible. In many of the 740 cases in which the clinical diagnosis has been made, not only 2 but even 3 or 4 of the other clinical criteria were found associated with the gait abnormality.

Alcohol was found in the urine of 381 cases, all but 9 of whom were included in the group of 1000 cases showing alcohol in the blood. In Table 4 are tabulated the number and percentage occur-

rence of the 5 designated clinical criteria in these 381 cases. An alcoholic odor to the breath was found in 88.8% (339 of the 381 cases). Gait and speech abnormalities were found in 287 and 267 cases, a percentage occurrence of 75.3 and 70.1 respectively. Dilated pupils occurred in 259 cases (68%) while a flushed face was found in the fewest number, 220 (57.7%). Using the same clinical criteria for the detection of drunkenness as previously outlined, a positive clinical diagnosis was made in 75.3% (283 cases). In only 4 instances was a gait abnormality encountered without a diagnosis of clinical intoxication being made.

TABLE 4.—NUMBER AND PERCENTAGE OCCURRENCE OF DESIGNATED CLINICAL CRITERIA IN 381 CASES WITH ALCOHOL IN THE URINE.

Clinical criterion.	Number positive clinical criterion.	Per cent positive clinical criterion.
Alcoholic odor	339	88.8
Abnormality gait or inability to walk	287	75.3
Abnormality speech or inability to talk	267	70.1
Pupils, dilated	259	68.0
Flushed face	220	57.7

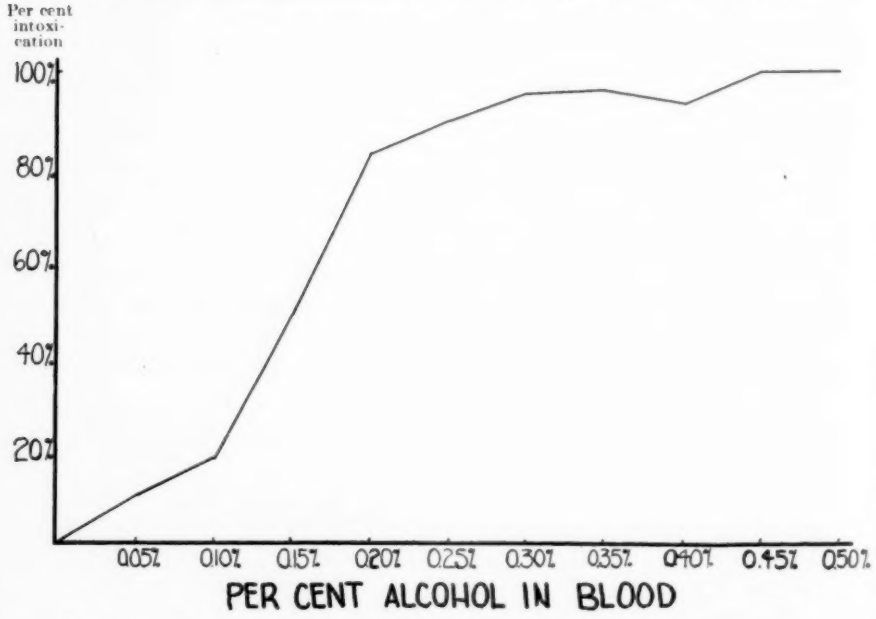
Chemical Results. 1. BLOOD. A. *Correlation of Occurrence of Acute Alcoholic Intoxication With Varying Alcoholic Concentrations.* The 1000 cases showing alcohol in the blood were divided into groups showing definite levels of alcoholic concentration, namely, 0.05% (including from 0.005 to 0.075%), 0.10% (from 0.075 to 0.125%), 0.15% (from 0.125 to 0.175%), 0.20%, and so on. The number and proportion of cases in each of the various groups are shown in Table 5. The largest number of cases, 330, occurred in the group 0.20% alcohol. A total of 779 cases occurred in the groups of 0.15 to 0.30% alcohol, inclusive. In the group 0.05% alcohol, were found 38 cases and 74 at 0.35%. Fifteen cases were found in the group 0.40% alcohol. Only 7 cases were found in the combined groups of 0.45 and 0.50% alcohol.

TABLE 5.—NUMBER AND PERCENTAGE OCCURRENCE OF ACUTE CLINICAL INTOXICATION AT VARYING GROUPS OF ALCOHOL CONCENTRATION.
(Blood—1000 cases.)

Groups alcohol concentration:	0.05 %.	0.10 %.	0.15 %.	0.20 %.	0.25 %.	0.30 %.	0.35 %.	0.40 %.	0.45 %.	0.50 %.	Total.
Total number of cases	38	87	132	330	176	141	74	15	5	2	1000
Number of cases intoxicated	4	16	61	276	158	133	71	14	5	2	740
Percentage cases intoxicated	10.5	18.4	47.0	83.6	90.0	95.1	96.0	93.3	100	100	74.0

Also in Table 5, and in Graph 1, the cases in which a clinical diagnosis of acute alcoholism was made are grouped at the various levels of alcoholic concentrations in the blood. Four cases (10%) of the 38 cases falling in the group at 0.05% alcohol were intoxi-

cated. In the group of 0.10% alcohol, 16 of 87 cases (18.4%) were inebriated. The incidence of drunkenness then rose rapidly; 47% in group 0.15% alcohol, 83.6% at 0.20%, and 90% at 0.25% alcohol. At 0.30% alcohol the incidence of inebriation was 95.1%. Intoxication was present in 96 and 93.3% of cases at groups 0.35 and 0.40% alcohol respectively. In the concenfration brackets 0.45 and 0.50% alcohol, all cases were drunk. Severe intoxication usually was present at 0.35 and 0.40% alcohol. At group 0.40% alcohol, only 1 of 15 cases was considered not intoxicated according to our standards while coma was present in 8 cases. Two individuals died at concentrations of 0.47 and 0.48% alcohol respectively

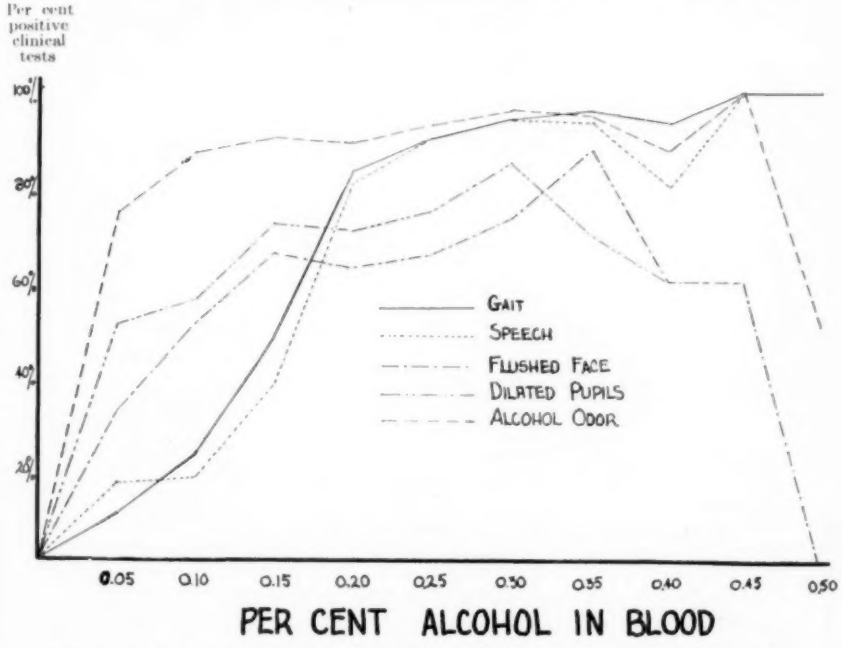


GRAPH 1.—Percentage occurrence of clinical intoxication at various concentrations alcohol; blood, 1000 cases.

from acute alcoholism as substantiated by postmortem findings. No cases with concentrations exceeding 0.50% alcohol were observed.

B. *Correlation of Designated Clinical Criteria With Varying Alcoholic Concentrations.* An analysis of the 1000 cases showing alcohol in the blood was made in respect to the occurrence of clinical criteria at the various alcoholic concentrations (Graph 2). The curves representing gait and speech abnormalities follow closely the curve of clinical intoxication as depicted in Graph 1. At the concentration groups 0.05 and 0.10% alcohol both gait and speech abnormalities were present in less than 20% of the cases. The percentage of occurrence at 0.15% alcohol was approximately 40% of the cases

and at 0.20% alcohol, approximately 80% of the cases. Both curves then gradually approached 100% which occurred in group 0.45% alcohol. In most instances, gait abnormality occurred slightly more frequently than did abnormality of speech. The incidence of alcoholic odor was high at all concentrations of alcohol, never dropping lower than 73% at group 0.05% alcohol. The incidence of dilated pupils and flushed face did not follow the curve representing the incidence of clinical intoxication. While the incidence of both of these criteria rose somewhat with increasing concentrations of alcohol (approximately 80% of cases at groups 0.30



GRAPH 2.—Percentage occurrence positive clinical tests at various concentrations alcohol; blood, 1000 cases.

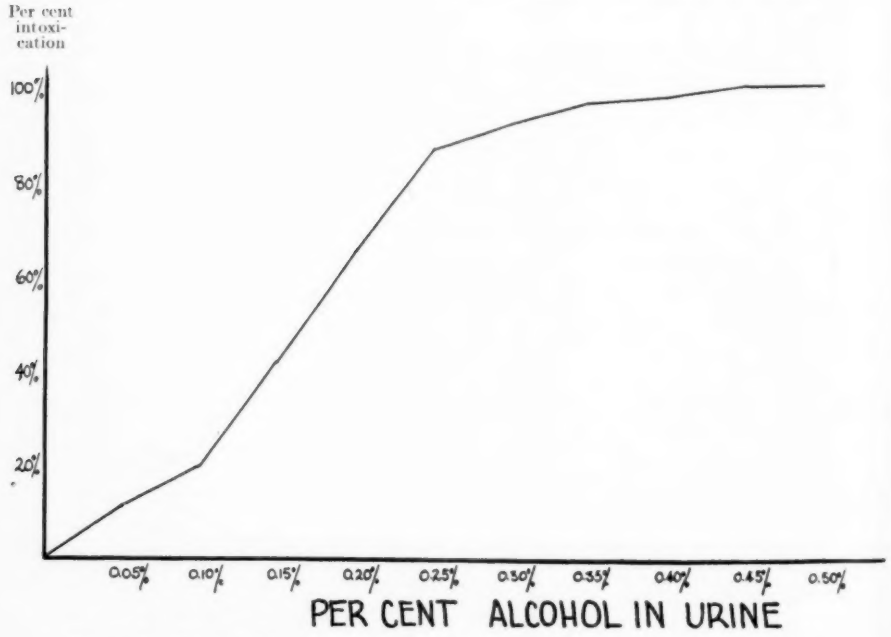
and 0.35% alcohol), their percentage occurrence decreased with still higher levels.

2. URINE. A. *Correlation of Occurrence of Acute Alcoholic Intoxication and Designated Clinical Criteria With Varying Alcoholic Concentrations.* Of the 381 cases showing a positive test for alcohol in the urine, 372 were included in the 1000 cases in which alcohol was found in the blood. No cases were observed with a positive urine and a negative blood or *vice versa*. The urinary concentration of alcohol was usually higher than that in the blood. The average ratio of the alcoholic concentration of the blood and urine in these 372 cases was blood to urine as 1 to 1.23 (range: from 1 to 2.3

to 1 to 1). In actual percentage of alcohol, the greatest variation was found in 1 case with 0.19% alcohol in the blood and 0.30% in the urine.

TABLE 6.—NUMBER AND PERCENTAGE OCCURRENCE OF ACUTE CLINICAL INTOXICATION AT VARYING GROUPS OF ALCOHOLIC CONCENTRATION.
(Urine—381 cases.)

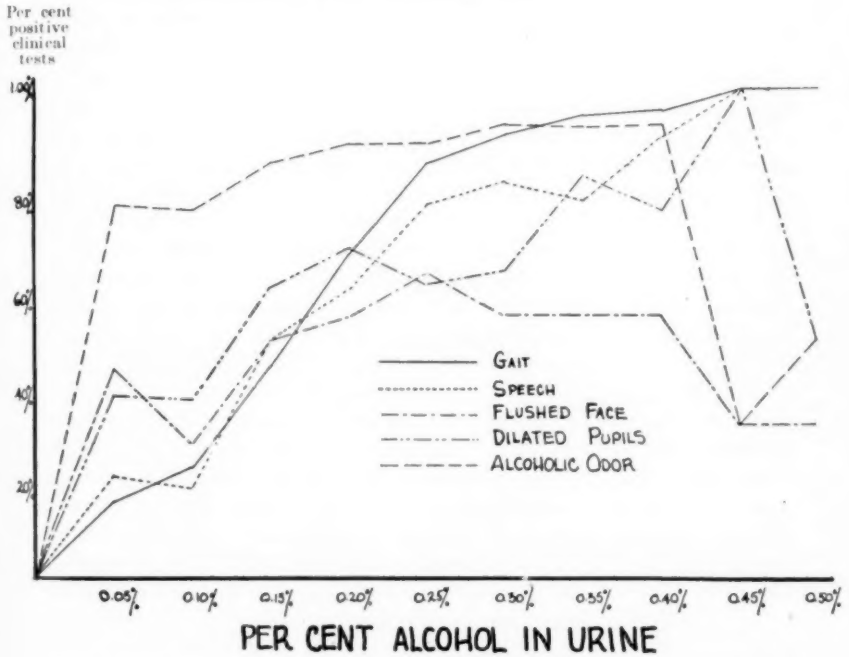
Groups alcohol concentration:	0.05 %.	0.10 %.	0.15 %.	0.20 %.	0.25 %.	0.30 %.	0.35 %.	0.40 %.	0.45 %.	0.50 %.	Total.
Total number of cases . .	18	26	36	61	66	95	44	30	3	2	381
Cases intoxicated . . .	2	5	15	40	57	88	42	29	3	2	283
Percentage cases intoxicated	11.3	19.2	41.7	65.0	86.4	92.6	95.5	96.7	100	100	75.3



GRAPH 3.—Percentage occurrence of clinical intoxication at various concentrations alcohol; urine, 381 cases.

The 381 cases were placed in various groups of alcoholic concentrations in a manner similar to that used in the blood (Table 6). The greatest number of cases were found at group 0.30% alcohol, a total of 95 (25%) of the cases. In the groups of 0.20 to 0.35% alcohol inclusive, there were 266 cases (70%). Below group 0.20% alcohol a total of 80 cases was found. Thirty-five cases were encountered in groups 0.40, 0.45 and 0.50% alcohol. No cases were observed showing a concentration above 0.50% alcohol.

The cases in which a clinical diagnosis of acute alcoholism was made are shown grouped at the various brackets of alcoholic concentration in the urine in Table 6 and Graph 3. A definite rise in the occurrence of inebriation is noted after a comparatively low incidence of from 10 to 19% of the cases in the groups 0.05 and 0.10% alcohol respectively, to 41 and 65% of the cases at groups 0.15 and 0.20% alcohol. At 0.25% alcohol, the percentage of intoxication had risen to 86%. At 0.30% alcohol, 88 of 95 individuals (92.6%) were drunk. The incidence rose slightly at 0.35 and 0.40% alcohol to 95 and 97% respectively, while at levels above this concentration all cases were intoxicated.



GRAPH 4.—Percentage occurrence positive clinical tests at various concentrations alcohol; urine, 381 cases.

An analysis of the urine series in respect to the occurrence of clinical criteria at various groups of alcohol concentration is shown in Graph 4. The curves representing gait and speech abnormalities closely follow the incidence of clinical intoxication as shown in Graph 3. An alcoholic odor was present in a high percentage of cases at all levels. The curves of dilated pupils and flushed face rises slightly higher with increasing concentrations of alcohol but drops somewhat at the higher levels.

Discussion. In the beginning of this study, it was found necessary to adopt definite criteria for the clinical diagnosis of acute

alcoholism, a procedure which apparently has not been regularly used in other studies. In general, however, loss of muscular coordination has been considered a necessary finding for the diagnosis. In an analysis of a series of this size, namely 1159 cases, the clinical diagnosis of acute alcoholism could be made consistently only on the basis of some definite stipulated combinations of physical findings. In this manner, individualization of the single case was avoided and a logical treatment of all cases in exactly the same manner was accomplished. Thus, a positive diagnosis has been made only upon gross physical departure from normal. We have required gait abnormality as an absolutely essential finding in association with any 2 of 4 other findings, namely, abnormality of speech, alcoholic odor of breath, flushed face and dilated pupils. In the determination of incoördination of locomotion, gross swaying, staggering or reeling must be present, ascertained by having the individual walk from one side of the room to the other. More delicate tests of incoördination, such as the finger-to-nose test, or to walk a straight line, have not been used, because such tests are difficult to evaluate and are of too sensitive a nature. The elimination of the personal equation in the determination of the type of speech was accomplished by having the patient answer to familiar questions only, such as his name, age, residence, and so on. In contradistinction, the other 3 findings were not subject to the human element at least to a great degree. The diagnosis of acute alcoholism as made upon these criteria becomes, it is believed, a definite entity, which would be corroborated by most examiners.

Of the 5 clinical criteria, an alcoholic odor occurred most frequently, 90% of the cases, whether clinical intoxication was diagnosed or not. The other 4 criteria were found in 60 to 75% of the cases. There was considerable variation of their incidence at the different groups of alcoholic concentration found in both blood and urine. No correlation was noted when comparing the incidence of alcoholic odor, flushed face and dilated pupils with the incidence of clinical intoxication. The number of cases showing flushed face and dilated pupils was relatively small at low concentrations of alcohol, but rose to higher levels at concentration groups of 0.20 to 0.35% alcohol inclusive. At concentrations exceeding 0.35% alcohol, dilated pupils and flushed face were not seen so frequently. Most of the cases at these high concentrations were in coma and had the well-known pale skin and constricted pupils of alcoholic coma. It would appear that these 3 findings, alcoholic odor, flushed face, and dilated pupils could be considered significant of drinking but not characteristic of drunkenness.

The curves showing the incidence of gait and speech abnormalities paralleled each other and followed closely the incidence of clinical intoxication. It might be supposed that the curve of gait abnormalities would approximate that of clinical intoxication be-

cause this criterion has been made essential for the diagnosis. The curve representing speech abnormality was similar to both gait abnormality and that of the incidence of clinical intoxication. Hence, it may be reasoned that both speech and gait abnormalities are characteristic not only of drinking but also of actual drunkenness.

That the differential diagnosis of acute alcoholism is difficult at times is evidenced by the 72 cases which at admission were alcohol-free, although a pre-admission diagnosis of acute alcoholism has been made. Particularly difficult is the diagnosis when the case is comatose. This was shown by the 32 cases, admitted in coma which were improperly diagnosed as due to alcohol. On the other hand, in such cases the possibility of alcohol being the etiologic agent must always be borne in mind. One such case may be used as an example. The police requested admission for a white male who was found lying unconscious in the street. After artificial respiration had been administered by the fire department, the patient was brought to the hospital with a diagnosis of heat stroke. At admission the possibility of alcoholic coma was suspected. The alcoholic concentration of the blood was 0.37%.

The correlation of acute alcoholism and the blood alcoholic concentration becomes valid only if the concentration of blood and brain alcohol shows a constant relationship. Experimental work in dogs by Harger *et al.*[2] in 1937 has shown that a constant relationship between blood and brain alcohol does exist at all periods up to 12 hours following ingestion of alcohol. No similar data have been submitted concerning a possible relationship to brain and urine alcohol.

In 372 cases in which both blood and urine examinations were available on the same patient the alcohol concentration of the urine was either equal to or higher than the concentration of alcohol in the blood. The average was blood to urine as 1 to 1.32. The reason for higher concentration of alcohol in the urine is not altogether clear.

In comparing the blood and urine determinations it is seen that the incidence of clinical intoxication is quite similar. Its incidence at groups 0.15 to 0.30% alcohol is somewhat lower in the urine than in the blood at similar levels. This lag is to be expected because of the ratio of alcohol in blood and urine already mentioned. At any rate, intoxication was found in all cases in both blood and urine in the group 0.45% alcohol. Because of the unpredictable ratio between blood and urine alcohol, a like situation is to be expected in a comparison between brain and urine alcohol. Therefore, the alcoholic content of the urine does not afford an altogether reliable indicator of the status of the other body tissues. It was noted, however, that while the ratio between urine and blood alcohol showed considerable variations at low concentrations of alcohol, at higher concentrations the ratio approached unity. The slight decrease in intoxication noted at group 0.40% alcohol in the blood

may be explained by the relatively small number of cases occurring at this level and is without significance.

Our findings as to the incidence of intoxication at various levels of alcoholic concentration correlate well, on the whole, with those of other studies. However, it was not until the concentration bracket of 0.45% alcohol in both blood and urine was reached that all patients were clinically intoxicated. This is in contradistinction to the findings of previous workers, who observed intoxication in 100% of cases at concentrations of 0.20 to 0.30% alcohol. The striking rise in the incidence of inebriation at levels of from 0.10 to 0.20% alcohol noted by Hoffman,[5] Widmark[11] and Schwarz,[9] and also by the smaller series of Bogen[1] and Harger,[3] are duplicated in this series.

There is no case in this series with a concentration above 0.50% alcohol in either blood or urine. Two deaths have occurred at 0.47 and 0.48% alcohol in the blood. When it is realized that at 0.40% alcohol, a concentration close to the lethal point, that an individual may show so little effects as to be adjudged sober by our criteria, or, on the other hand, that he may be in coma at this same level, it becomes evident that there exists a marked variation in the individual's reaction to alcohol. This variation may perhaps be explained by tolerance of the body cells to alcohol as in this paper only definite concentrations of alcohol have been considered and not the amount of alcoholic beverage consumed in attaining a given concentration. Newman[8] has shown that a tolerance may be produced in dogs by making them "chronic alcoholic" from the daily ingestion of large quantities of alcohol. These animals exhibited less effects from a given concentration of alcohol in the blood than did normal dogs brought to the same concentration. Most of the cases in this series were presumably chronic alcoholics and would be expected to show a tolerance to alcohol as compared to the neophyte or occasional drinker. While most cases were drunk at concentrations of 0.35% alcohol, we have had 1 case unaffected by a concentration of 0.40% alcohol as already stated. Hence, the limit of tolerance might be placed at 0.45% alcohol. On the other hand, intoxication in the occasional drinker occurs at considerably lower concentrations since the experimental feeding of alcohol to this type of individual[6] has resulted in intoxication, according to our standards, at concentrations as low as 0.075% alcohol.

Summary. 1. A correlation was made of the clinical findings and the content of alcohol in the blood of 1150 cases admitted to the Buffalo City Hospital with a pre-admission diagnosis of acute alcoholism. Alcohol was found in the blood of 1000 cases. In 372 of these cases, the urine was also obtained. A total of 381 urines, all showing alcohol, were examined.

2. Of the 1000 cases with alcohol in the blood, 779 (77.9%) were found in the concentration groups of 0.15 to 0.30% alcohol inclusive.

Of the 381 cases in which the urine was examined, 266 (70%) fell in concentration brackets of 0.20 to 0.35% alcohol inclusive.

3. Employing the criteria for the diagnosis of acute alcoholic intoxication as outlined, clinical intoxication was found in the blood series in approximately 10% of the cases at the concentration group of 0.05% alcohol; in 18% at 0.10% alcohol; 47% at 0.15% alcohol; 83% at 0.20% alcohol; 90% at 0.25% alcohol; and 95% at 0.30% alcohol. Intoxication was present in 100% of cases in the concentration group of 0.45% alcohol. No cases were observed above 0.50% alcohol in either blood or urine.

4. Incidence of clinical intoxication in the urine series approximated that found in the blood series, although in general a lag was noted, most marked at concentrations of 0.15 to 0.30% alcohol. Intoxication was found in all cases at 0.45% alcohol.

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STUDIES IN ALCOHOL.

II. Experimental Feeding of Alcohol to Non-alcoholic Individuals.

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An attempt has been made to correlate the clinical manifestations of acute clinical intoxication occurring when known amounts of alcohol were fed with the various blood alcoholic concentrations so obtained. A review of the literature has revealed no studies of an exactly similar nature.

Method. Ethyl alcohol, in concentrations of approximately 10%, was fed to 20 young normal adults, in 4 groups of 5 members each. All were either occasional drinkers or, in a few instances, total abstainers. Group 1 received 1 cc. per kg. of body weight; Group 2, 1.25 cc.; Group 3, 1.5 cc.; and Group 4, 2 cc. Ingestion was begun in the morning on a fasting stomach or after a light breakfast and was completed in 45 minutes or less. Samples of blood from the median basilic vein were taken regularly at 1-, 2-, 3-, 4-, 6-, 8-, 12- and 24-hour intervals, the first sample being taken

exactly 1 hour after the first drink. The blood alcohol content was determined by the method devised by Heise.[2] In addition, the individuals were examined for acute alcoholic intoxication using the clinical criteria as previously outlined.[3]

Results. Graphs 1, 2, 3 and 4 show the concentration of alcohol in the blood of each of the members of the four groups at the various time intervals. In all cases, the highest concentration occurred 2 hours after the beginning of ingestion and was 0.10, 0.13, 0.15 and 0.19% alcohol respectively in the four groups. In all four groups, the concentration of alcohol fell somewhat abruptly from the second to the sixth hour after ingestion, after which it then decreased more gradually. In all cases in Groups 1 and 2, the blood was alcohol-free in 8 and 12 hours respectively, whereas in Groups 3 and 4, the blood was alcohol-free in 24 hours.

TABLE 1.—ALCOHOL, 1 CC. PER KG. BODY WEIGHT.
(Group 1.)

Case No.:	1.	2.	3.	4.	5.
Alcoholic odor	+	+	+	+	+
Flushed face	+	+	+	+	+
Dilated pupils	+	0	+	0	+
Speech abnormalities	+	0	0	+	0
Gait abnormalities	+	+	0	0	0
Intoxicated	Yes	Yes	No	No	No

TABLE 2.—ALCOHOL, 1.25 CC. PER KG. BODY WEIGHT.
(Group 2.)

Case No.:	6.	7.	8.	9.	10.
Alcoholic odor	+	+	+	+	+
Flushed face	+	+	+	0	+
Dilated pupils	0	0	+	+	+
Speech abnormality	+	+	+	0	0
Gait abnormality	0	+	+	+	+
Intoxicated	No	Yes	Yes	Yes	Yes

TABLE 3.—ALCOHOL, 1.5 CC. PER KG. BODY WEIGHT.
(Group 3.)

Case No.:	11.	12.	13.	14.	15.
Alcoholic odor	+	+	+	+	+
Flushed face	+	+	+	0	+
Dilated pupils	0	0	0	+	+
Slurred speech	0	+	0	0	0
Gait abnormality	0	+	+	0	0
Intoxicated	No	Yes	Yes	No	No

TABLE 4.—ALCOHOL, 2 CC. PER KG. BODY WEIGHT.
(Group 4.)

Case No.:	16.	17.	18.	19.	20.
Alcoholic odor	+	+	+	+	+
Flushed face	0	0	+	0	0
Dilated pupils	0	+	0	+	+
Slurred speech	+	+	+	+	+
Gait abnormality	+	+	+	+	+
Intoxicated	Yes	Yes	Yes	Yes	Yes

All 20 cases were examined for evidence of clinical intoxication. Tables 1, 2, 3 and 4 show the incidence of the 5 clinical criteria and

of clinical intoxication in all members of the groups. All cases showed an alcoholic odor to the breath and in 14 cases a flushed face was present. Dilated pupils and slurred speech occurred in 11 cases, while gross reeling, swaying, or staggering was found in 13 cases. Using the clinical criteria for intoxication as described previously, a diagnosis of acute alcoholism was made in 13 cases, or an incidence of 65%. In general, the greatest degree of intoxication in any given case was noted when the concentration of alcohol was highest in the blood stream, namely 2 hours after ingestion. In the intoxicated cases, all 5 criteria were found in 2 cases; 4 criteria were present in 7 cases, while in 4 cases only 3 criteria were noted. Of the 7 non-intoxicated, in none of whom a gait abnormality was found, 4 cases exhibited 3 of the other 4 criteria while the other 3 cases had but 2 present. In addition, all exhibited evidence of mental instability, talkativeness, excitability and lack of self-control.

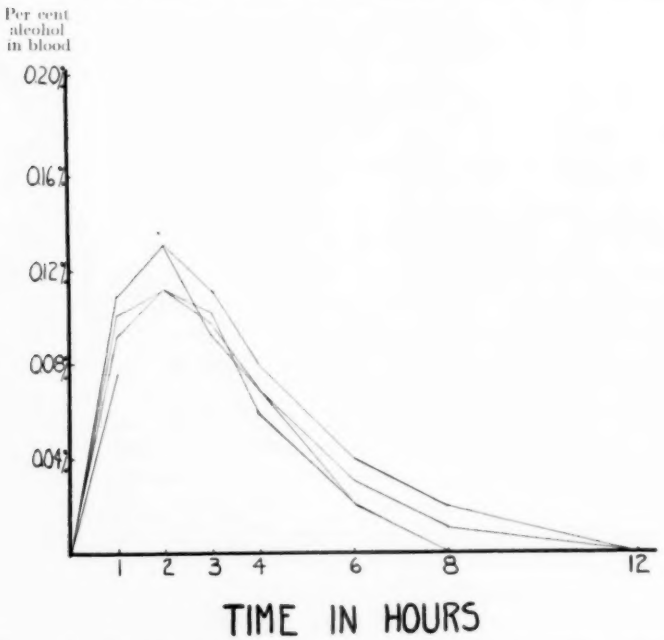
Two cases of Group 1 became intoxicated at concentrations of blood alcohol of 0.09 and 0.10% alcohol. Four of the 5 persons in Group 2 were drunk at concentrations of 0.075, 0.11 and 0.13% (2 cases). Only 2 of 5 cases in Group 3 became inebriated, both at 0.15% alcohol. All 5 cases of Group 4 were intoxicated at concentrations of 0.18 and 0.19%.

TABLE 5.—INCIDENCE OF ACUTE CLINICAL INTOXICATION AT DEFINITE GROUPS OF BLOOD ALCOHOL CONCENTRATION—COMPARISON OF EXPERIMENTAL AND HOSPITAL GROUPS.

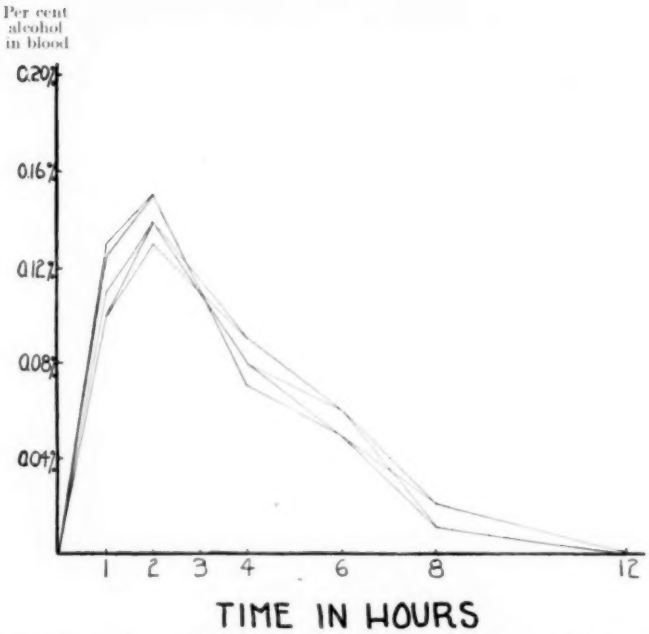
	Experimental.			Hospital.		
Concentration of alcohol.	No. of cases.	No. of cases intoxicated.	Percentage cases intoxicated.	No. of cases.	No. of cases intoxicated.	Percentage cases intoxicated.
0.075–0.125%	8	4	50	87	16	18
0.125–0.175%	7	4	57	132	61	47
0.175–0.225%	5	5	100	330	276	83

Discussion. The incidence of clinical intoxication at definite groups of alcoholic concentration in the blood in this series is compared to that in the larger group as shown in Table 5. The more frequent occurrence of clinical intoxication (50%) at relatively low concentrations of alcohol in the blood (0.075 to 0.125%), found in these studies is in contrast to the lower incidence of the condition noted at similar concentrations in the larger group, namely 18%. Such a difference may be significant in spite of the great disproportion in the number of cases in the two groups. It may be supposed that the chief variance of these two groups depends upon their alcoholic habits. Members of the groups which were fed alcohol were occasional or non-drinkers, whereas those of the larger group were, for the most part, chronic alcoholics, the majority having known alcoholic histories of long standing. Thus, it would appear logical to explain the variation in their reaction to alcohol on the basis of an acquired tolerance, a status which has been shown to

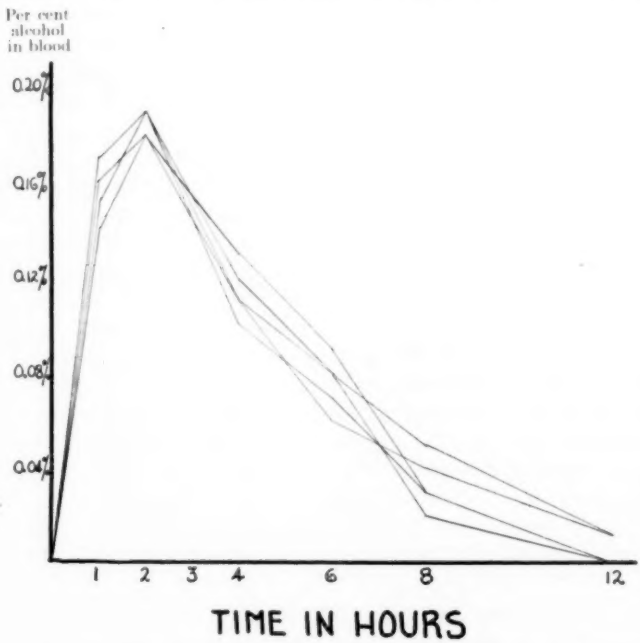
GRAPH 1.—Experimental feeding; alcohol, 1.0 cc./kg. body weight. Group I.



GRAPH 2.—Experimental feeding; alcohol, 1.25 cc./kg. body weight. Group II.



GRAPH 3.—Experimental feeding; alcohol, 1.5 cc./kg. body weight. Group III.



GRAPH 4.—Experimental feeding; alcohol, 2 cc. kg. body weight. Group IV.

exist in experimental animals by Newman.[4] In addition, it appears that the occasional drinker may possess some tolerance in comparison to the non-drinker. Four non-drinkers were intoxicated at levels of 0.075 to 0.11% alcohol while 3 cases, occasional drinkers, were not intoxicated at 0.14 and 0.15% alcohol.

It has been noted that all chemical data have been tabulated in terms of percentage of alcohol by weight per 100 cc. of blood. In order to convert to alcohol per 100 gm. of blood, the concentration of alcohol must be multiplied by $\frac{1.00}{1.06}$ as the specific gravity of human blood is 1.06. Since the specific gravity of ethyl alcohol is 0.79, 1 cc. of alcohol weighs only 0.79 gm. It will be seen that when 1 cc. of alcohol is fed per kg. of body weight, the maximum concentration of alcohol which could be attained, assuming that complete absorption and uniform diffusion of alcohol throughout the body tissues has occurred, could be no higher than 0.079% alcohol by weight per 100 gm. of tissue. Actually at 2 hours, concentrations in the blood as high as 0.10% alcohol (per 100 cc. blood) were found. This percentage, calculated to 100 gm. blood, would be lowered to 0.094%, which is still above the highest possible theoretical value. This variation between the calculated and determined values indirectly confirms the experimental work of Harger,[1] who has recently shown that there is a lag in the diffusion of alcohol in skeletal muscle until 3 hours after ingestion, diffusion being uniform after that time. In addition, the initial sharp rise in the concentration of blood alcohol following ingestion, the peak of which is reached 2 hours after ingestion, and the subsequent rapid fall is explained by this so-called muscle lag.

It has been shown in Graphs 1, 2, 3 and 4 that when 1, 1.25, 1.5 and 2 cc. of ethyl alcohol are fed per kg. of body weight, the percentage of alcohol by weight per 100 cc. of blood approximates at 2 hours, 0.10, 0.125, 0.15 and 0.20% respectively. It would seem, therefore, that in order to calculate the smallest amount of alcohol ingested necessary to produce a given concentration of alcohol in the blood, a basis of cc./kg. rather than gm./kg. be used. After a period of 3 hours the muscle lag need not be considered, at that time calculations might be made on a basis of gm./kg. It is assumed in such calculations that all alcohol be consumed in an hour or less on a relatively empty stomach in a concentration of 10%. Whether the above assumptions under the same conditions hold true for the chronic alcoholic is rather doubtful. Jungmichel, Schmidt, Fleming and Stotz, Bernhard and Goldberg (quoted by Newman) and Newman and Card[4] have shown that the concentration of alcohol in the blood is slightly higher in chronic alcoholics than in the non-alcoholics when the same amounts of alcohol are fed.

From the work of Harger, which as yet has not been confirmed, it would appear that all tissues except skeletal muscle show an

immediate and constant diffusion of alcohol, although this ratio may not always be unity. The most important relationship, that of blood to brain, appears to be constant at all times regardless of the time after the ingestion of alcohol. It follows, then, that the concentration of alcohol in the brain may be predicted if the concentration in the blood is known. Since intoxication is dependant upon the concentration of alcohol in the central nervous system, it would seem logical, therefore, to predicate intoxication on a determination of the alcohol content of the blood. Harger's work, however, was performed on non-alcoholic animals. Whether the constant relationship between blood and brain alcohol exists in chronic alcoholics is as yet undetermined.

Conclusions. 1. The blood alcohol content was determined in 20 normal volunteers at regular intervals following the ingestion of 1, 1.25, 1.5 and 2 cc. of alcohol per kg. of body weight.

2. Acute clinical intoxication occurred in 50% of cases in which the alcohol concentration in the blood varied from 0.075 to 0.125%; in 57% in concentrations from 0.125 to 0.175%; and in 100% in concentrations from 0.175 to 0.225% alcohol.

3. The incidence of acute clinical intoxication in these so-called normal individuals at low alcoholic concentrations was much higher than was the incidence at similar concentrations in a larger group consisting primarily of chronic alcoholics.

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THE RED CELL MASS IN POLYCYTHEMIA IN RELATION TO DIAGNOSIS AND TREATMENT.

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Polycythemia vera is primarily an increase in the number of erythrocytes. This increase is the only constant abnormality in the disease and is responsible for the symptoms and physical findings. The spleen enlarges in storing and disposing of some of the excess red cells; the cyanosis depends on the slow circulatory rate resulting from the high viscosity. The treatment of polycythemia is based on disposing of the excess of red cells by hemolysis or bleeding. The diagnosis and treatment thus require accurate data concerning the erythrocytes.

The red cells per unit volume of blood are always increased in polycythemia vera. An increase is also observed, however, in symptomatic polycythemia due to an interference with oxygenation

of hemoglobin, so a diagnosis of polycythemia vera cannot be made on an increased number of cells per cubic millimeter alone. The blood volume is a valuable aid in differentiating the symptomatic and idiopathic types. In symptomatic polycythemia the blood volume is seldom increased; in polycythemia vera the blood volume is always increased. Very little emphasis has been placed on this characteristic increase in blood volume in polycythemia vera even in such complete reviews as those of Harrop[1] and Parkes-Weber and Bode.[2] Blood-volume determinations in a few cases have been recorded over many years by a number of workers. The only large series is the 50 cases reported by Rowntree, Brown and Roth.[3] The blood volume may be increased in a wide variety of clinical conditions, however, so an increase is not limited to polycythemia vera.

Method. In making the blood-volume determinations reported herewith, the colorimetric method of Rowntree, Brown and Roth,[3] using Congo red (National Anilin, Schultz, No. 307), has been employed. A freshly made 1.5% solution of the dye is sterilized by bringing to the boiling point twice. The exact amount of solution delivered from the 18-cc. graduation mark on a 20-cc. record syringe has been determined and each patient is given this amount intravenously. Exactly 4 minutes after the dye is injected, blood is withdrawn from the other arm without the use of a tourniquet. A 1.4% solution of sodium oxalate is used as the anticoagulant for the hematocrit readings. The red cell mass is simply calculated from the hematocrit reading and the total blood volume.

The blood findings in 20 consecutive patients with polycythemia vera have been studied to determine the most significant indicator of changes in the red cells on which the disease depends. The data are recorded in Table 1. For comparison, the findings in a group of patients who presented either a high red cell count or an increased blood volume due to symptomatic polycythemia are shown in Table 2. The red cell count per cubic millimeter, the total blood volume, the total red cell mass, the total red cell count, and the blood volume and red cell mass per kilogram of body weight are greater than normal in every patient with polycythemia vera. In the symptomatic group, the red cell count per cubic millimeter, the total red cell count, the total blood volume, the total red cell mass, or the blood volume per kilogram may be increased but there is never a significant increase in the red cell mass per kilogram.

The data in the two groups have been analyzed with respect to the following possible indicators of variation in the red cells:

1. Red cell count per cubic millimeter which measures the number of cells per unit volume only.

2. Total red cell count, which depends on the number per unit volume and the total blood volume but does not recognize the mean cell volume.

3. Total blood volume, which measures both cells and plasma and varies with body weight.

TABLE 1.—BLOOD FINDINGS IN POLYCYTHEMIA VERA.

Number.	Wt. (kg.).	Red cell count per c.mm. (millions).	Hematocrit reading (vol. %).	Total volume. Whole blood (cc.).	Plasma (cc.).	Red cell mass (cc.).	Blood volume per kg. (cc.).	Red cell mass per kg. (cc.).	Total number red cells (trillions).
				Female.					
Mean of 10 normals	56	4.50	40	3702	2220	1482	66.4	26.4	16.7
1	58	5.89	48	5600	2912	2688	98.0	47.2	33.0
2	58	5.44	47	6090	3228	2862	105.0	49.3	33.1
3	58	6.51	56	5443	2558	2885	94.0	50.0	35.4
4	82	6.60	60	6082	2432	3650	74.0	43.6	40.1
5	52	7.68	65	6063	2122	3941	117.0	75.8	45.6
6	58	10.60	67	7659	2068	5551	132.0	96.0	81.2
				Male.					
Mean of 10 normals	77	5.00	45.5	4960	2634	2326	64.4	30.0	24.8
7	75	6.09	51	6319	3096	3223	84.3	43.0	38.5
8	62	6.12	57	5965	2365	3600	97.8	59.0	36.4
9	75	7.10	63	6811	2520	4291	90.0	56.0	48.4
10	75	6.90	64	7135	2568	4564	92.1	59.0	49.2
11	80	7.22	62	7590	2884	4706	95.0	59.0	54.8
12	100	7.20	67	7553	2492	5061	75.0	50.0	54.4
13	74	9.25	61	8836	3446	5400	119.0	72.9	81.7
14	71	8.62	70	8083	2425	5658	117.0	82.0	69.7
15	64	8.33	73	7768	2098	5670	121.0	88.6	66.5
16	70	7.60	71	8138	2360	5778	117.0	84.2	61.8
17	58	7.66	72	8025	2247	5778	138.0	100.0	61.5
18	60	9.20	72	8296	2323	5973	133.0	100.0	76.3
19	80	7.90	70	8557	2467	5990	107.0	74.0	66.6
20	82	9.55	78	10454	2300	8154	127.5	100.0	100.8

TABLE 2.—BLOOD FINDINGS IN PATIENTS WITH HIGH RED CELL COUNT OR HIGH BLOOD VOLUME ONLY.

Number.	Weight (kg.).	Red cell count per c.mm. (millions).	Hematocrit reading (vol. %).	Total volume. Whole blood (cc.).	Plasma (cc.).	Red cell mass (cc.)	Blood volume per kg. (cc.).	Red cell mass per kg. cc.	Total number red cells (trillions).	Diagnosis.
						Female.				
Mean of 10 normals	56	4.50	40	3702	2220	1482	66.4	26.4	16.7	Normal
21	77	6.43	52	5040	2419	2621	65.0	33.8	31.4	
22	55	6.62	40	3728	2267	1461	68.0	26.0	23.1	
23	42	3.88	30	4156	2909	1247	100.1	29.7	16.1	Rheumatoid arthritis
24	54	4.49	35	4781	3107	1674	88.0	31.0	21.5	Hypertension; aortic insufficiency
25	46	4.16	32	3881	2600	1281	84.4	27.9	16.1	Rheumatoid arthritis
						Male.				
Mean of 10 normals	77	5.00	45.5	4960	2634	2326	64.4	30.0	24.8	Normal
26	79	6.07	50	5667	2833	2834	72.0	35.4	34.4	Obesity; dermatitis
27	132	6.15	55	6320	3223	3097	48.0	23.6	37.9	Obesity; angiospasm
28	84	6.23	48	5421	2819	2602	65.0	31.4	33.8	Obesity
29	59	4.20	40	5609	3365	2234	95.1	23.5	23.6	Multiple myeloma
30	56	3.19	33	6253	4189	2064	112.6	37.2	19.9	Rheumatoid arthritis

4. Total red cell mass, which recognizes all variants of the red cell only, number, total blood volume, hematocrit reading, and mean cell volume, but varies with body weight.

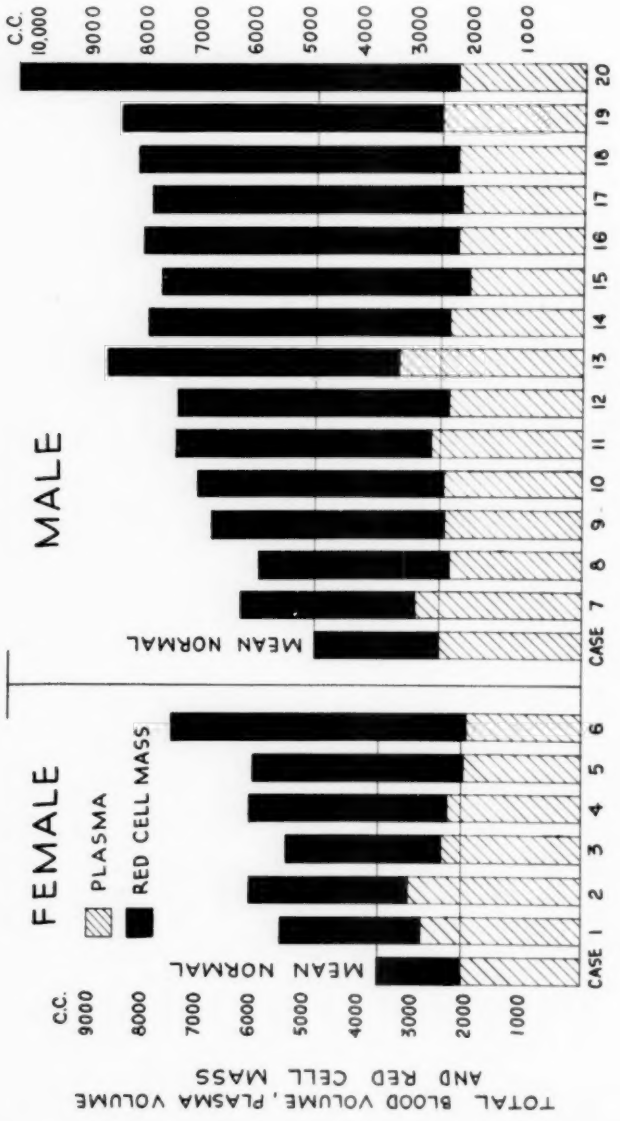

Fig. 1

5. Blood volume per kilogram, which measures both cells and plasma in relation to body weight.

6. Red cell mass per kilogram, which measures all variants of the red cell in relation to body weight.

The total blood volume, the plasma volume, and the total red cell mass for the 20 patients with polycythemia vera are shown in Figure 1 in relation to normal. The significant point here is the

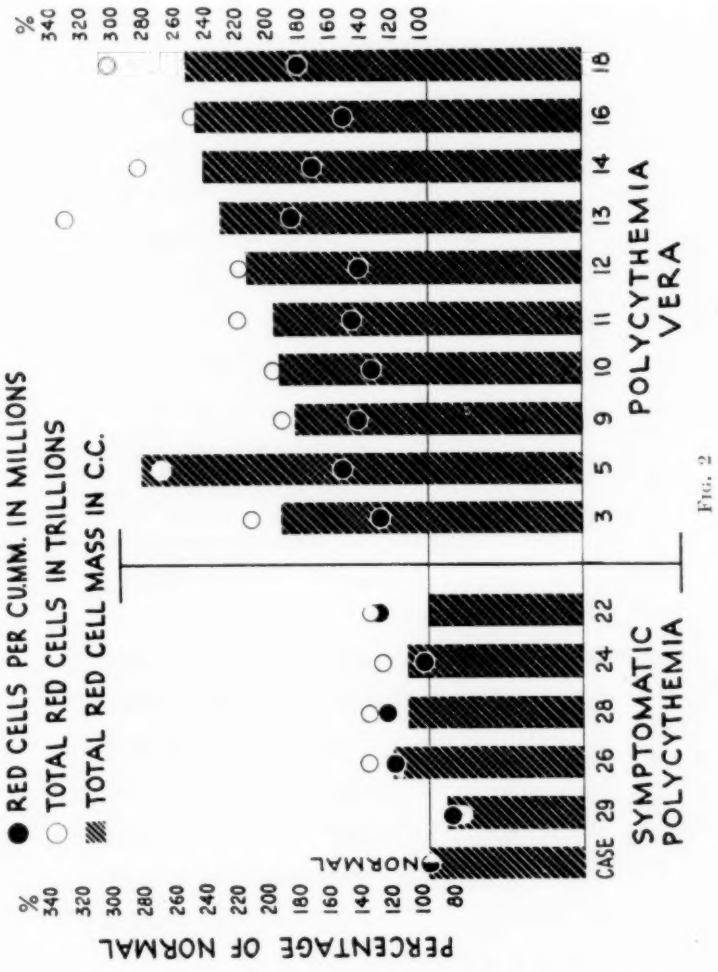
PERCENTAGE OF NORMAL
% 340 320 300 280 260 240 220 200 180 160 140 120 100 80
NORMAL
CASE 29 26 28 24 22 3 5 9 10 11 12 13 14 16 18
SYMPTOMATIC POLYCYTHEMIA
POLYCYTHEMIA VERA
● RED CELLS PER CU.MM. IN MILLIONS
○ TOTAL RED CELLS IN TRILLIONS
▨ TOTAL RED CELL MASS IN C.C.

Fig. 2

remarkably little variation in plasma volume even with a great increase in total blood volume. The characteristic increase in blood volume is thus due almost entirely to an increase in cell mass. In Figure 2 the total red cell count, the red cell count per cubic millimeter, and the total red cell mass are compared. All data are figured in percentage relative to normal. In the idiopathic poly-

cythemia group, it is apparent the red cell count per cubic millimeter reflects very inadequately the total increase in red cells, since

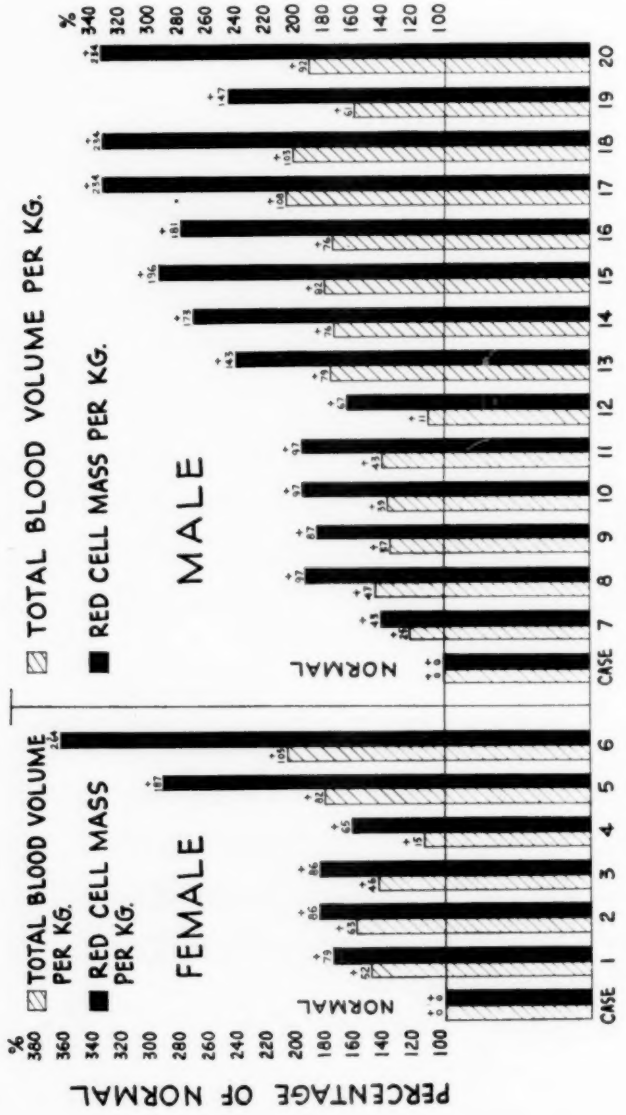

Fig. 3

the cell count is constantly much lower than the red cell mass. The total red cell count parallels more closely the variation in red cell mass but is usually relatively too high because the mean red

cell volume is frequently less than normal. In the cases of symptomatic polycythemia, the red cell mass is seldom significantly in-

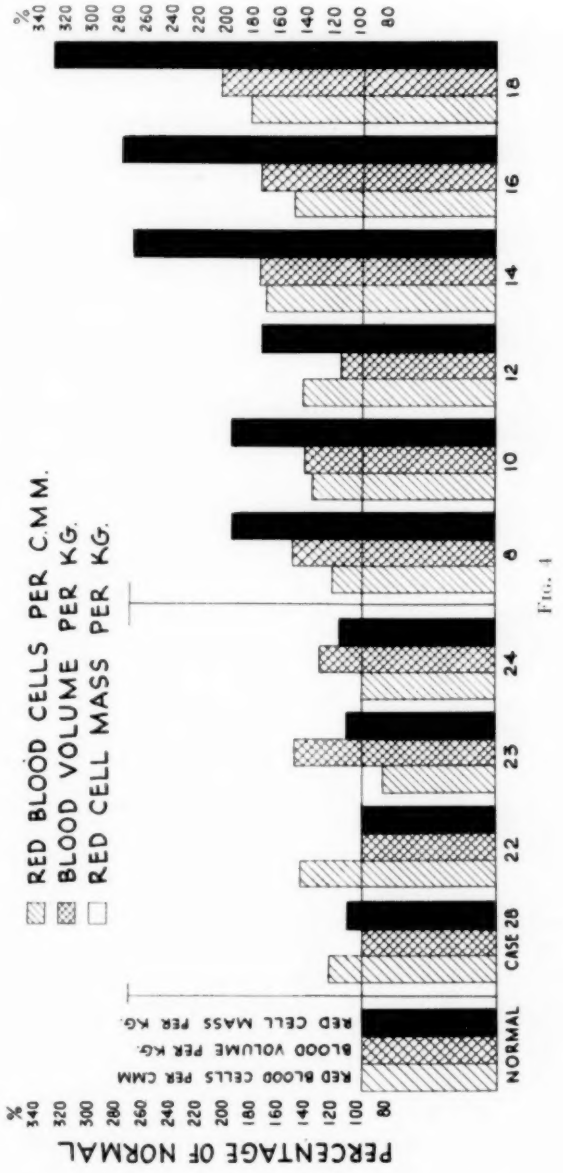

Fig. 1

creased, so here both the red cell count and total red cells are usually relatively too high.

In Figure 3 the total blood volume per kilogram and the red cell mass per kilogram are compared. Since the plasma volume is relatively constant, the percentage increase in red cell mass is very much greater than is the increase in total blood volume per kilogram.

In Figure 4 the red cell count per cubic millimeter and the blood volume and red cell mass per kilogram are compared in symptomatic polycythemia and polycythemia vera. In symptomatic polycythemia, the red cell mass per kilogram is not increased even with a high red cell count per cubic millimeter or a high blood volume per kilogram. If the blood volume is high, the blood volume per kilogram is higher than the red cell mass per kilogram. In polycythemia vera the red cell mass per kilogram is constantly high and relatively much higher than the red cell count per cubic millimeter or the blood volume per kilogram. It is apparent that the red cell mass per kilogram is: 1, the most sensitive and reliable indicator of total changes in the red cell in polycythemia; 2, constantly increased in polycythemia vera; and, 3, seldom increased in symptomatic polycythemia. The diagnosis of polycythemia vera is not justified without demonstrating such an increase.

TABLE 3.—POLYCYTHEMIA VERA—CHANGES IN RED CELLS IN RELATION TO TREATMENT.

No.	Wt. (kg.).	Date.	Red cell count per c.mm. (millions).	Hematocrit reading (vol. %).	Total volume.			Blood volume per kg. (cc.).	Red cell mass per kg. (cc.).	Total number red cells (trillions).
					Whole blood (cc.).	Plasma (cc.).	Red cell mass (cc.).			
14	71	Normal for wt.	5.00	45	4572	2442	2130	64.4	30.0	22.85
	71	12-30-32	8.62	68	8083	2525	5558	117	78.3	75.86
	70	10- 5-37	7.90	60	7712	3085	4627	110	66.1	60.90
	72	11- 5-37	6.30	50	6916	3358	3358	93	49.4	43.57
	72	11-18-37	6.12	49	6449	3289	3160	90	44.0	39.47
	72	12- 6-37	6.54	53	6236	2931	3305	87	46.0	42.76
	72	1-17-38	5.82	49	6837	3487	3360	95	46.7	39.79
	76	2-28-38	6.18	50	6118	3059	3059	81	42.5	38.24
	76	3-17-38	6.15	49	5790	2953	2837	76	37.0	35.60

In treating polycythemia vera, the excess of red cells must be destroyed by hemolysis or removed by venesection. If a hemolytic agent such as phenylhydrazine or acetylphenylhydrazine is employed, the amount of drug tolerated depends on the relative mass of the red cell as the hemolytic reaction is a quantitative one. Since the red cell count does not show the relative mass of red cells, this cannot be depended on as a guide in treatment. Here the most desirable measure is the total red cell mass as shown for one patient in Figure 5. The data for this patient are recorded in Table 3. The normal red cell mass for each patient is calculated and an

attempt made to keep the red cells at this level by appropriate treatment.

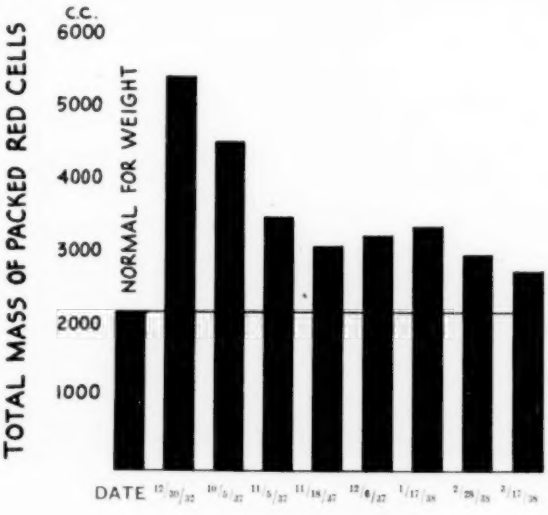

FIG. 5

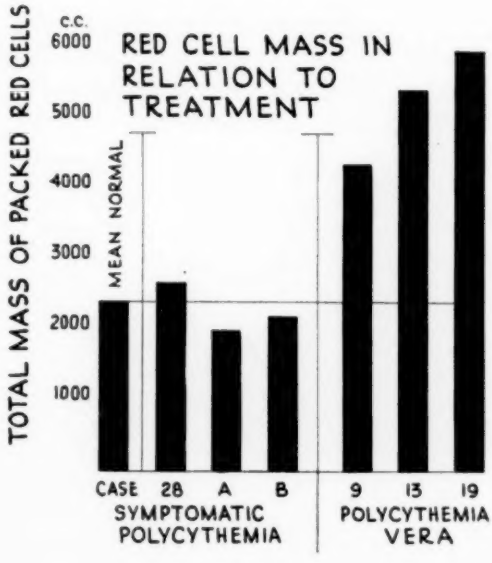

FIG. 6

The disastrous results seen in treating some patients on the basis of the red cell count alone is explained by the great variation in

total red cell mass. The actual red cell mass in 3 patients in whom a marked anemia quickly developed following treatment with acetylphenylhydrazine is shown in Figure 6. These patients all had high red cell counts per cubic millimeter so polycythemia vera was suspected. In 1, the total red cell mass was determined before treatment was given; in 2 others, after the blood had returned to the normal level. In each instance, the total red cell mass was normal so there was no real excess of red cells to dispose of. It is thus easy to see why a small amount of drug produced such a marked anemia.

Conclusions. The total blood volume is constantly increased in polycythemia vera. The increase concerns the red cells almost entirely since the volume of plasma is seldom greater than normal.

The red cell count per cubic millimeter does not measure accurately the total increase in red cells as it is relatively too low. The total red cell count is usually relatively too high due to a decrease in mean cell volume.

The red cell mass per kilogram is the most sensitive indicator of changes in the red cells. The red cell mass is constantly high in polycythemia vera and not significantly changed in symptomatic polycythemia.

The treatment of polycythemia vera should be based on the total red cell mass.

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THE USE OF MAPHARSEN IN THE TREATMENT OF MALARIA.

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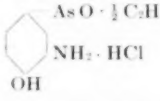
The use of arsphenamines in the treatment of malaria was introduced almost as soon as their therapeutic efficacy in syphilis and spirochetal diseases was demonstrated. Werner[1a,b] in 1910 described in detail the effect of intravenous and intramuscular injections of salvarsan (606) in tertian and estivo-autumnal malaria. He found that a single injection of 0.6 gm. caused disappearance of the parasites within 24 hours in almost all cases of tertian malaria and he found no recidives within several weeks. In estivo-autumnal malaria only half the cases responded favorably immediately after the injection and most of these recurred after several days. Since that time there have been innumerable publications on the use of salvarsan, neosalvarsan and other arsenated benzine compounds in malaria.

In some institutions, where therapeutic malaria is used extensively, neosalvarsan has been used to terminate the malaria chills and fever.

In the author's experience at least half of these cases would recur if only a single injection of neosalvarsan were given without the additional use of quinine or atabrine.

The introduction of mapharsen in treatment of syphilis naturally suggests its use in protozoan infections, particularly since the assay of the therapeutic efficacy of the drug is made in rat trypanosomiasis. For these reasons the use of mapharsen in treatment of therapeutic malaria was begun early in 1937. A fortunate opportunity also presented itself for its use in the naturally occurring disease in a case of chronic recurring malaria of about 8 months' standing.

Mapharsen is a trivalent arsenical which is exceedingly toxic and potent and is thought to be the effective breakdown product of the arsphenamines in the body. Chemically, it is meta-amino parahydroxy phenyl arsine oxide.[2]



Its toxicity and therapeutic index have been thoroughly studied by Tatum and Cooper[3] and others. Its chief advantage seems to be constancy of chemical composition and as a result of this a relatively unvarying therapeutic index. Besides this the therapeutic dose is only one-tenth as great as the average dose of neoarsphenamine and consequently contains proportionately less arsenic.

The use of mapharsen in human syphilis has been thoroughly studied by Foerster and his coworkers[1] and by Gruhzit.[2] Since these original publications numerous authors have added data concerning the effectiveness of this drug. Its effectiveness in experimental trypanosomiasis is at least equivalent to that of the arsphenamines in the range of therapeutic dosage. A careful search of the literature reveals no reference to the use of mapharsen in the treatment of malaria previously. The present study deals with its effectiveness in this disease.

The technique of application of this remedy differs in no way from the administration in syphilis. According to the patient's weight 0.04 to 0.06 gm. are injected intravenously in the fasting state. Injections may be repeated at 5 to 7-day intervals. In most cases (over 90%), a single injection suffices to terminate the malaria permanently, but to insure against recurrences it is well to give 3 or 4 injections at the proper intervals (Table 1). In therapeutic malaria as usually used for dementia paralytica a course of 8 to 10 injections will usually be given for the sake of its antisyphilitic value and at the same time the malaria is permanently eradicated.

Mapharsen has been found to be much less toxic in debilitated patients than neoarsphenamine or even quinine. It seems likewise safer to use than atabrine. No toxic manifestations have been found in over 20 cases. Even malaria associated with severe leukopenia responded only favorably and with an increase in the leukocytes.

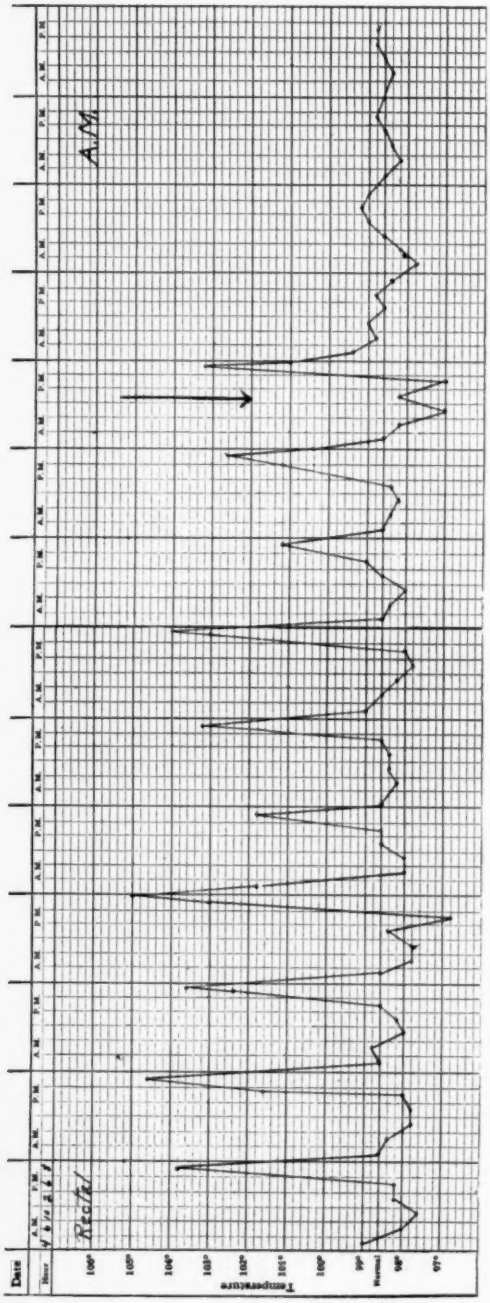


FIG. 1

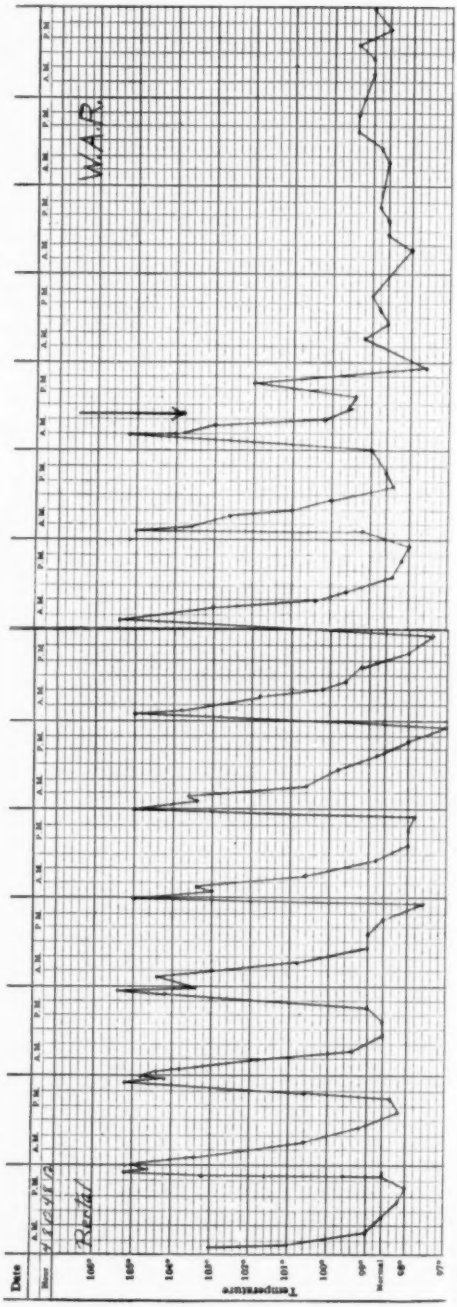


FIG. 2

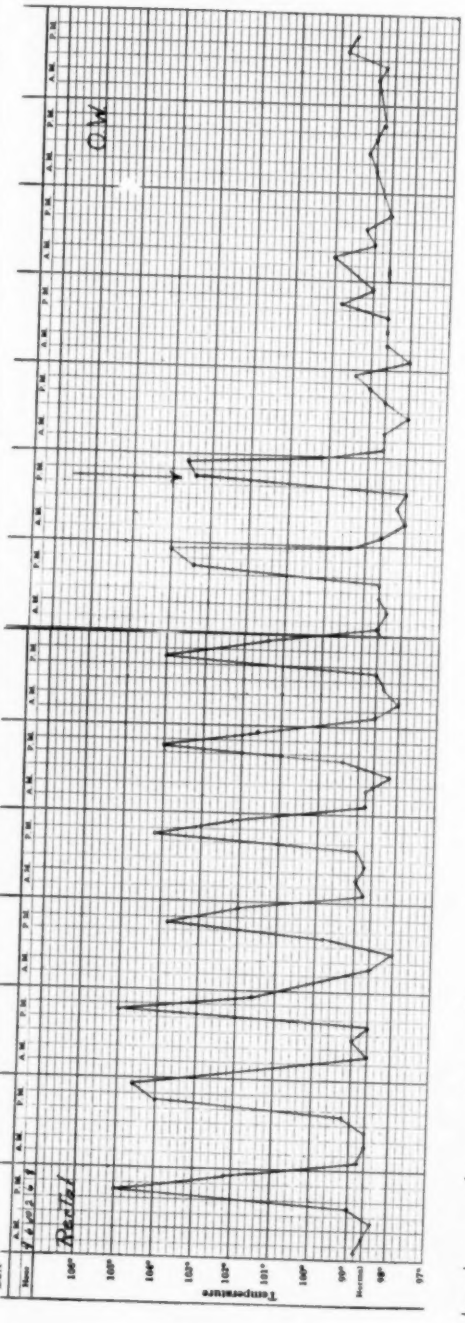
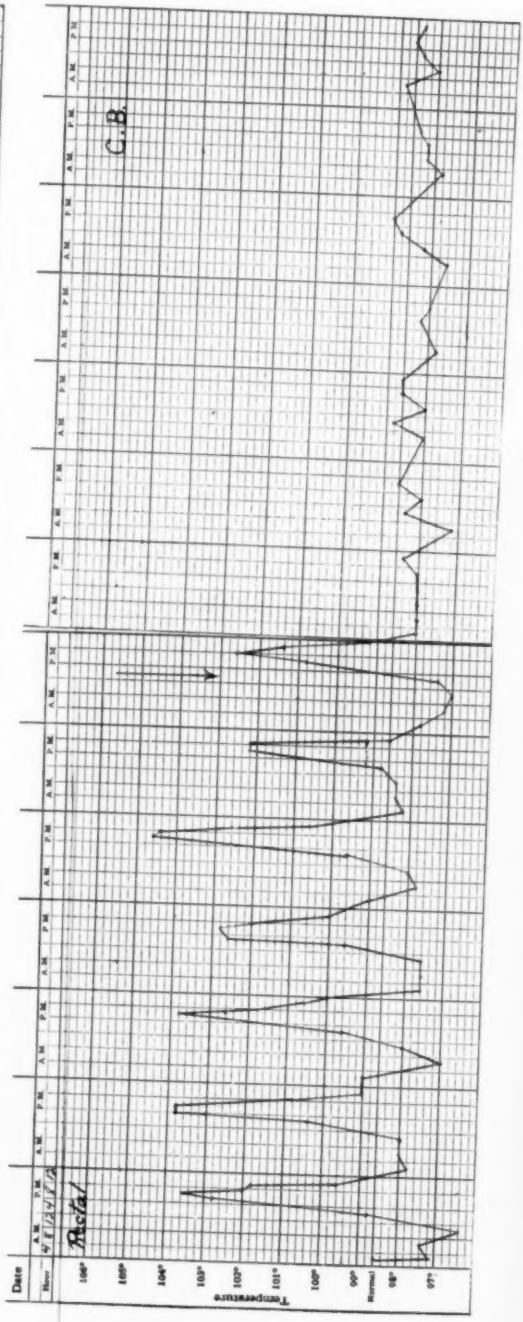

C.W.
Rectal
Date
Hour
A.M. P.M.
Temperature
Normal

FIG. 3


C.B.
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Date
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Temperature
Normal

FIG. 4

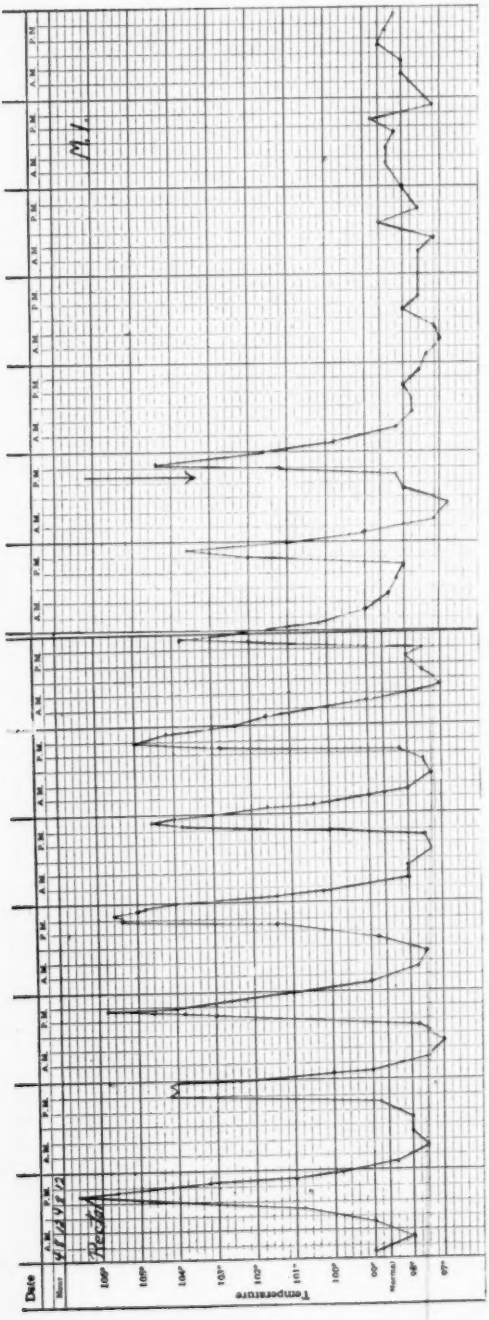

FIG. 5

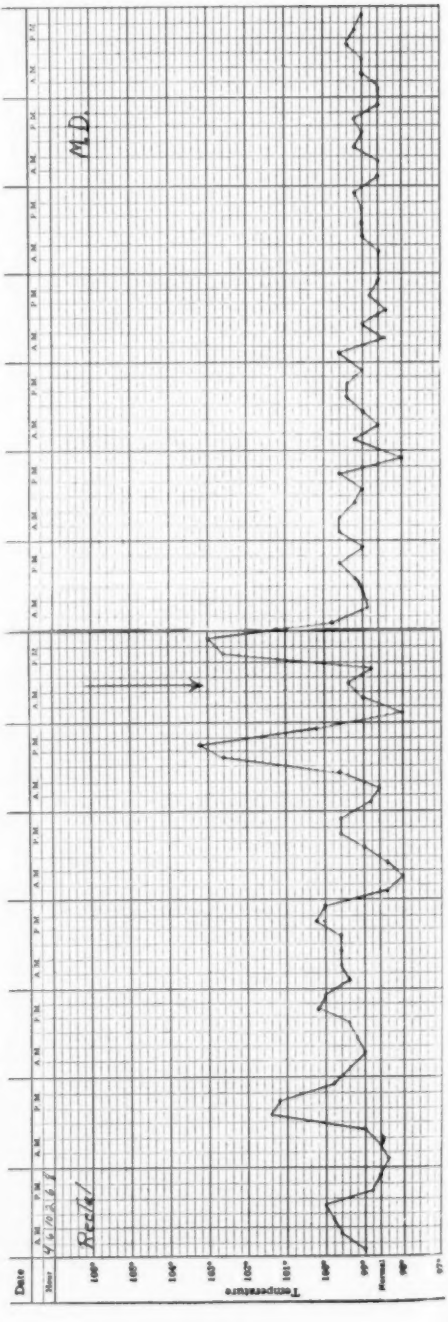

FIG. 6

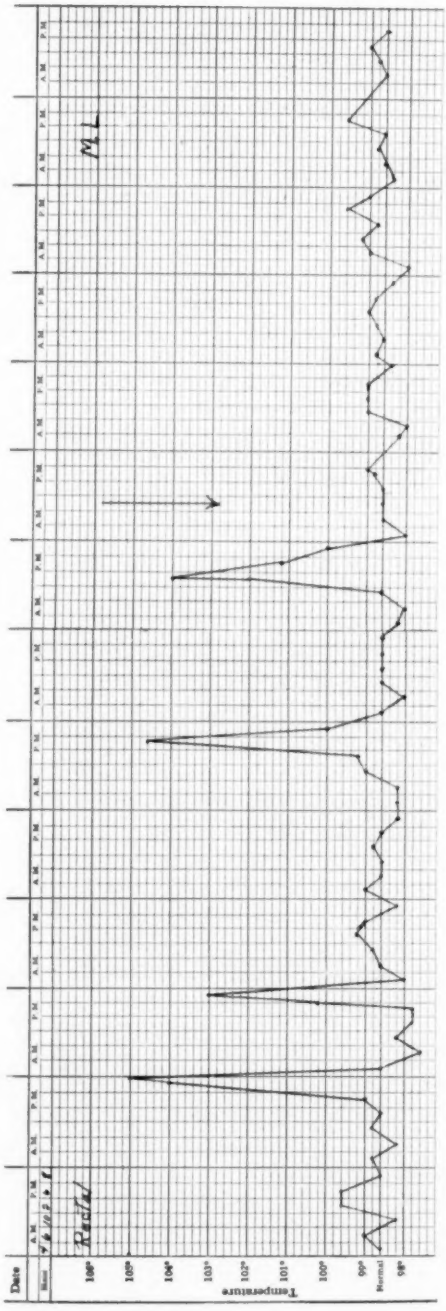

FIG. 7

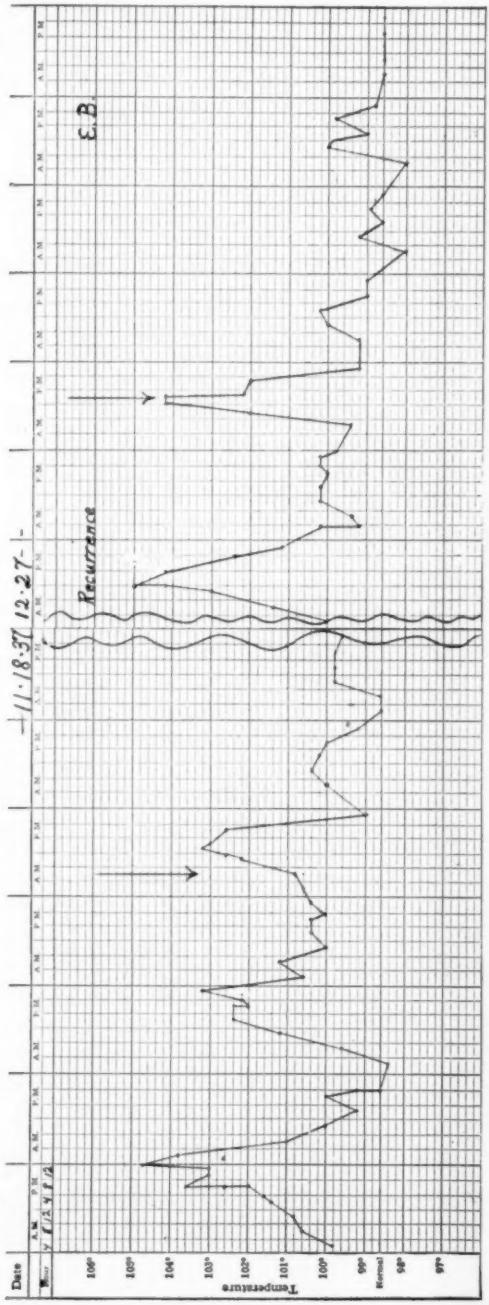

FIG. 8

FIGS. 1 to 7.—The behavior of the malarial fever following termination with mapharsen at the points indicated by the arrows.

FIG. 8.—The effectiveness of mapharsen in spite of the recurrence a month after the original infection was terminated.

TABLE 1.—RESULTS OF MAPHARSEN INJECTIONS.

Case.	Patient.	No. of injections.	Immediate result.	Recurrence	Effect of retreatment.
1	O.L.	11	Good		
2	W.R.	11	"		
3	M.L.	1	"		
4	M.D.	11	"		
5	L.G.	11	"		
6	W.L.	1	"		
7	O.W.	11	"		
8	F.P.	1	"		
9	G.M.	11	"		
10	A.M.	11	"		
11	H.T.	1	"		
12	C.B.	11	"		
13	N.P.	1	"		
14	M.I.	1	"		
15	F.T.	1	"		
16	J.H.	11	"		
17	A.G.	1	"		
18	G.T.	1	"		
19	A.K.	1	"	+	Good
20	G.V.	1	"		
21	C.K.	4	"		
22	E.B.	1	"	+	Good
23	F.C.	1	"		
24	J.C.	1	"		

Recurrences after mapharsen are rare and are encountered only in severe cases which in this series were believed to have been allowed to run longer than was advisable. Only 2 instances are on record and 1 of these is illustrated in the accompanying charts.

The disappearance of the parasites is almost immediate. After 24 hours it is only rarely that a disintegrating form can be found in the blood smears. Splenomegaly begins to disappear almost as rapidly. Within a day the spleen is usually appreciably smaller and within 3 or 4 days has receded behind the costal margin.

Examination of the charts reveals that the timing of the injection to a great extent governs the occurrence or nonoccurrence of a chill following treatment. It is seen that if a chill is to be expected in less than 24 hours it usually occurs in spite of the injection, but if the chill is not due for more than 24 hours or if the injection is given at the height of a chill, no subsequent chill will occur. It has been found that the injection of mapharsen even when the temperature is markedly elevated is without danger.

The therapeutic efficacy of mapharsen and its low toxicity make it an ideal remedy for use in malaria, whether of therapeutic or natural origin. Compared with quinine it is immeasurably more effective. It is probably no more effective than atabrine, but the relative ease of its administration, the comfort of the patient in not having to take a somewhat irritant drug and the absence of danger of unpleasant yellow discoloration of the skin or toxic changes in the viscera again make mapharsen the drug of choice.

Unfortunately, no opportunity has been had to test the efficacy of this remedy in estivo-autumnal malaria. It is most important

to determine what effect if any it will have on the notoriously resistant gametocytes of malignant malaria.

The charts will serve as case reports for the therapeutic malaria cases treated with mapharsen. The case of naturally occurring malaria will be recited briefly:

Case Report. C. K., aged 33, white, male, contracted malaria probably late in Aug., 1936, while travelling through Arkansas marshes on an automobile tour. The patient gave a history of a very stormy febrile course prolonged in spite of treatment to 5 weeks. Following this, the patient would have recurrences at intervals of 1 or 2 weeks sometimes in spite of taking 10 or 15 grains of quinine daily. He had been found sensitive to atabrine according to the physician taking care of him at that time. The recurrences usually lasted from 2 to 5 days and were characterized by fever of irregular type from 101 to 103° F., aching bones and severe malaise. The patient was first seen in May, 1937, during one of these recurrences. Parasites were numerous in the peripheral blood. Following injection of 0.05 gm. of mapharsen the symptoms rapidly disappeared. Later the patient was given 3 more injections of mapharsen at weekly intervals with quinine for 3 days of each week for 3 weeks. He had no recurrence following the first injection of mapharsen and has remained symptom free and free of parasites for 8 months.

Conclusions. 1. Mapharsen, a recently introduced arsenated benzine compound for use in syphilis, has been used with strikingly good effect in tertian malaria both of natural origin and artificially inoculated.

2. The effectiveness of this drug and its safety compare favorably with other commonly used malaricidal compounds effective on the asexual stages of the parasites.

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THE USE OF 2 (p-AMINOBENZENESULPHONAMIDO) PYRIDINE IN THE TREATMENT OF PNEUMONIA.

A Preliminary Report.

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During the past few months there have appeared in the British medical literature encouraging reports on the use of a new sulphanilamide derivative, M. & B. 693 (2 [p-aminobenzenesulphonamido] pyridine) in the treatment of pneumonia. We have begun to use

this material* in pneumonia patients admitted to several Philadelphia hospitals.

Experimental work, as reported by Whitby,[9] showed that the action of M. & B. 693 was similar to that of sulphanilamide in hemolytic streptococcus and meningococcus infections in mice. It was found that the drug had a definite action on pneumococcus Types I, VII and VIII, and to a lesser extent on Types II, III and V. Whitby observed that the drug caused degeneration and subsequent disappearance of the capsule of the pneumococcus. M. & B. 693 is reported to possess a low toxicity for animals, does not produce porphyrinuria, and is active in relatively small doses. Wien[10] found the toxicity of M. & B. 693 to be approximately 25% of that of sulphanilamide in mice. Even when administered to dogs and cats in large doses over a considerable period, no untoward reactions were observed. Fleming,[5] in *in vitro* studies, observed that the drug was antibacterial against both hemolytic streptococcus and pneumococcus; and that growth was retarded in human blood in concentrations which, it is reasonable to suppose, can be obtained therapeutically. In the concentrations which he used, however, it was not bactericidal except in the presence of leukocytes. He found that the action of the drug was greater in immunized blood, which suggested that the best clinical results may be obtained in combination with the use of type-specific sera.

Among the early clinical reports was that of Telling and Oliver,[8] who reported 2 cases of pneumonia treated successfully with M. & B. 693. The only evidence of toxicity which they observed was a moderate degree of cyanosis in 1 case. Bacteriologic study of their patients confirmed the earlier experimental studies that the drug caused a decapsulation and consequent loss of type specificity of the organism. The largest number of cases and the most complete study has been reported by Evans and Gaisford.[4] These investigators treated 100 cases of pneumonia with M. & B. 693, and used as a control group 100 cases which received various other forms of therapy. All cases in both groups were unselected, except for 3 that died within 24 hours after admission. The mortality rate in the group treated with M. & B. 693 was 8%, as compared to 27% in the control series. Of the 8 fatalities in the treated group, 6 received less than the minimal adequate dosage. The method of dosage in the majority of cases was the oral administration of an initial dose of 2 gm., followed every 4 hours with 1 gm., until a total of 25 gm. of the drug had been given. As much as 9 gm. was given during the first 24 hours to some of the more severe cases. No constant effect on the hematopoietic system was noted, although in 3 cases that survived the leukocytes fell to 5000. The only other evidence of toxicity was the presence of cyanosis in approximately 25% of the cases treated with large amounts of the

* M. & B. 693, manufactured by the English firm of May & Baker, was supplied to us through the courtesy of Merck & Co.

drug. There was no evidence of renal damage as determined by urine analysis in all treated cases and autopsy in those that died. Christie[1] reported a successfully treated case, and observed no toxic effects other than slight cyanosis. Other workers[2,3,6,7] have recently published data concerning the use of M. & B. 693 in gonococcus and meningococcus infections and have not mentioned any serious toxic reactions.

During the past few weeks we have had the opportunity of observing the effect of M. & B. 693 in 4 cases of pneumonia, in 1 of which both the drug and type specific serum were used. All 4 recovered. We wish in this brief report to record 2 of the patients treated only with the drug.

Case Reports. Case 1.—A. J., a 29-year-old white male, was admitted to the medical service of Dr. Samuel Lowenberg at the Philadelphia General Hospital on August 15, 1938. Except for a slight head cold of several weeks' duration the patient had been in good health until 6 days before admission, at which time he complained of general malaise, loss of appetite and chilliness. On the following day there was fever and pain in the right chest, with rusty sputum appearing 2 days later.

Physical examination revealed an acutely ill white man with marked dyspnea, moderate cyanosis and limitation of movement of the right chest. The tongue was heavily coated and over the right upper chest anteriorly was percussion dullness, increased tactile fremitus and vocal resonance, tubular breathing, whispered pectoriloquy and a few fine moist râles. The abdomen was moderately distended. The diagnosis of right upper and right middle lobe pneumonia was made and confirmed by Roentgen ray examination on the same day. The sputum, on typing and culture, revealed a predominance of pneumococci Type I. The blood culture was negative. See Chart I for leukocyte counts, dosage of drug (M. & B. 693), temperature, respiration and pulse readings.

The patient received an initial dose of 2 gm. (M. & B. 693) which was followed by 1 gm. every 4 hours thereafter until 16 gm. had been given. During the next 2 days the patient received 1 gm. every 6 hours for 5 doses, making a total of 25 gm. in all. The only evidence of drug toxicity was an attack of vomiting following the first 12 gm. of the drug. At the time of the fall of temperature, 24 hours after beginning the drug, the patient felt greatly improved and from that time on made an uneventful recovery. The physical findings presented evidence of resolution about the 10th day of the illness and at the time of discharge no signs of lung involvement were detectable. Chest Roentgen ray at that time was also negative. Routine urine studies throughout the illness were essentially negative.

Aside from the usual routine care given pneumonia cases the patient received no therapy other than M. & B. 693.

Case 2.—C. B., a colored male, aged 24, was well until several days before admission, when he contracted a rather severe head cold. Two days later, August 17, 1938, he experienced a sudden, sharp pain in the left chest, followed the next morning by shortness of breath, cough, rusty sputum and sores on the lips. On August 19 the patient was admitted to Dr. David Riesman's service at the Philadelphia General Hospital.

Physical examination revealed a well-developed male negro in acute respiratory distress, who was coughing up a moderate amount of blood-tinged sputum. There were several herpetic lesions on the lower lip. The left chest presented definite limitation of movement and over the left upper lobe there was dullness to percussion, increased tactile fremitus and vocal resonance, prolonged breath sounds and a friction rub. The diag-

nosis of left upper lobe pneumonia was made. The sputum showed a predominance of Type VIII pneumococci on typing and culture. Blood culture taken the following morning was reported as negative. Repeated urine analyses all negative (see Chart I).

This patient was treated in the same manner as Case 1, except that the drug was discontinued after 21 gm. had been given.

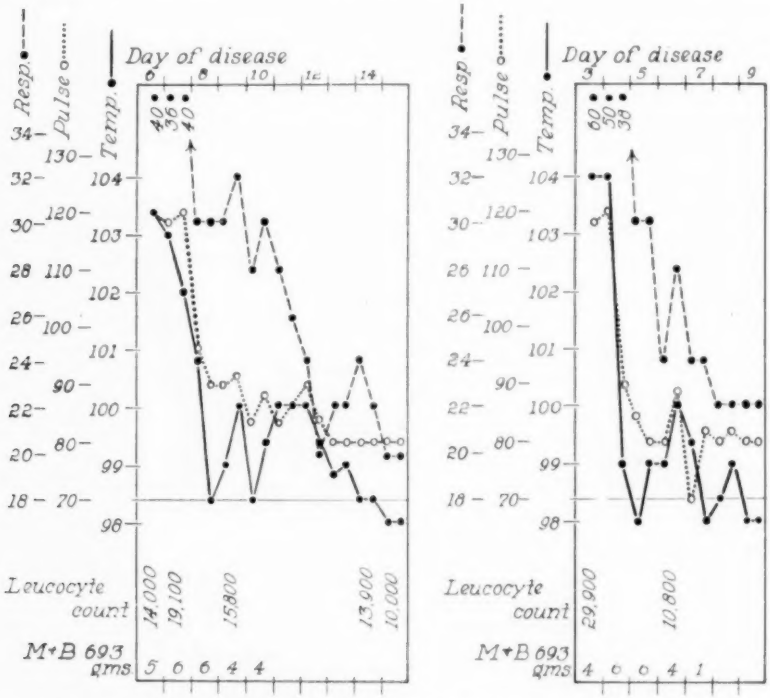

CHART I.—Leukocyte counts, dosage of drug (M. & B. 693), temperature, respiration and pulse readings.

There were no signs of toxicity attributable to the specific medication. Physical examination on the third day revealed bronchial breath sounds as well as many fine moist râles over the left upper lobe. The patient left the hospital on August 25, after an uneventful recovery. At the time of discharge Roentgen ray examination of the chest was negative. No other form of therapy was used except the usual routine measures in such cases.

Discussion. A review of the animal experiments and clinical studies which have been made with M. & B. 693 suggest that this drug has a direct effect upon the pneumococcus, in that it causes capsular degeneration and ultimate decapsulation of the organism with a resultant loss of type specificity. Studies *in vitro* suggest that any bactericidal effect which the drug possesses is dependent upon the presence of leukocytes, and there is some evidence that the drug may be more effective when combined with specific sera. The toxic reactions caused by M. & B. 693 are apparently no more

frequent than those encountered with sulphanilamide, and according to the majority of investigators, are much less severe. Those most commonly noted being moderate cyanosis and occasional vomiting. In Case 1 vomiting occurred following the administration of the first 12 gm. of the drug, but did not reappear even though the medication was continued. In the series of 100 cases reported by Evans and Gaisford,[4] 3 instances of mild leukopenia were recorded without fatality. There was no evidence in our patients that the drug affected bone-marrow activity. M. & B. 693 is administered orally, and is usually followed in 24 hours by a marked drop in temperature. A slowing of pulse and respiration accompanies this fall in temperature.

From the clinical and experimental studies already reported, and from our limited experience, we believe that the drug should receive a thorough trial in this country. This we plan to do.

Summary. 1. A new chemotherapeutic agent, M. & B. 693, said to be beneficial in the treatment of pneumococcus pneumonia, has recently been reported.

2. Reported experimental and clinical observations suggest that this drug has a definite effect upon the capsule of the pneumococcus.

3. The toxic manifestations of the compound appear to be relatively less than those of sulphanilamide.

4. Our limited experience with M. & B. 693 would suggest that it deserves an extended trial.

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PARTIAL AND COMPLETE HEART BLOCK IN ACUTE CORONARY ARTERY OCCLUSION.

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Introduction. In the present report we submit a detailed analysis of the disturbances in auriculoventricular conduction in 375 cases

of coronary artery occlusion, including a consideration of partial and complete heart block and simple prolongation of the *P-R* interval. In previous papers[68a,b] a similar analysis has been made of the other arrhythmias.

It has usually been thought that heart block was very rare.[4,90,99] Close scrutiny of the literature, however, has revealed a considerable number of cases, which leads to the conclusion that the association of heart block and coronary occlusion is not so infrequent as was thought.

In 1876, in the first diagnosis of coronary thrombosis suggested at the bedside and confirmed at necropsy, Hammer[41] was struck by the very slow heart rate of the patient, only 8 beats per minute. The significance of this escaped him but it is almost certain that complete heart block existed. Ten years later Huchard[48] recorded a case of Stokes-Adams syndrome associated with "angina pectoris." Other early reports of heart block and coronary artery occlusion were made by Jellick, *et al.*[49] and Gallavardin and Dufour.[30] In 1913 and 1914 Oppenheimer and his colleagues[74,75] made the first careful anatomic studies of the hearts in 4 cases of Stokes-Adams syndrome and found that in 2 of them the syndrome was the result of occlusion of one or more coronary arteries.

The first clinically recognized cases of coronary artery thrombosis associated with complete heart block and the Stokes-Adams syndrome were described by Levine and Tranter[62] in 1918 and Gallavardin[29] in 1922. Since then numerous reports of single instances of heart block in coronary thrombosis have appeared in the literature [1,3,9,10,12,14,15,20,25–28,32,39,42–44,52,57,59,65,71,72,78,82–84,86,88,89,93,94] comprising more than 35 cases described in detail. Kerr[55] collected 5 cases.

Recently Schwartz[87] presented 15 cases of *A–V* dissociation and Stokes-Adams syndrome in coronary artery occlusion which he had personally observed. Such an experience is unique, for no other author has reported such a large series. An analysis of approximately 1500 unselected cases of coronary artery occlusion included in 17 fairly large series reported during the last 15 years,[2,21–24,46,47,50,61,77,79,81,85,91,93,96,98] reveals that the incidence of complete heart block varied from 0.7 to 10%. The highest incidence, 10%, is probably not typical since it was derived from two small series, 19 and 30 cases respectively, and included only fatal cases examined postmortem. Omitting these two small series, the incidence varied from 0.7 to 4%, the average being 1.5%; the number of cases of complete heart block totalled 21. Less attention has been paid to partial heart block, including *P–R* prolongation and dropped beats, probably because the clinical course is less spectacular than that of complete block. There have been only occasional case reports of partial block,[3,11,13,43,55,73,93] but the incidence in the above quoted series was 2.5%.

Numerous attempts have been made to produce heart block experimentally by ligating the arteries to the conduction system but the results have been conflicting. When the septal artery alone was ligated in the dog, infarction of the septum occurred without heart block.[8,21,45,52,76] On the other hand, "mass ligation," to include the anastomotic vessels, uniformly resulted in all grades of heart block.[51,60,101] Similar results were obtained by experimental coronary embolism with lycopodium.[21,40] In monkeys, in which the vascularization of the septum is similar to that of man, DeWaart and his associates[95] produced heart block by ligation of the right coronary artery which gives off the septal artery, but not by ligation of the left coronary artery.

*Prolonged P-R Interval.** Simple prolongation of the *P-R* interval to 0.20 of a second or longer was observed in 60 (one-sixth) of the 375 patients with coronary artery occlusion who were studied (Table 1). The ratio of males to females in this group was 4:1,

TABLE 1.—*A-V* HEART BLOCK IN 375 CASES OF CORONARY ARTERY OCCLUSION.

	Prolonged *P-R*.	Partial heart block.	Complete heart block.	Normal *P-R*, no arrhythmia.
Number	60 (16%)	6	6	263
Average age (years)	55.5	62	59	56
Sex—Male:Female	4:1	1:1	1:5	4:1
Mortality	15%	2 (33%)	4 (67%)	24%
Attack—1st	57%	5 (83%)	2 (33%)	52%
Multiple	43%	1 (17%)	4 (67%)	48%
Hypertension	66%	3 (50%)	6 (100%)	65%
Enlarged heart	63%	3 (50%)	5 (84%)	60%
Heart failure	66%	5 (84%)	6 (100%)	72%

identical with that in the general series. Similarly, the average age and the incidence of previous attacks, hypertension, cardiac enlargement and heart failure were practically the same as in the patients without *P-R* prolongation. The mortality rate in the patients with *P-R* prolongation, 15%, was actually lower than in the entire series, 24%. It appears therefore that the presence of simple *P-R* prolongation exerted no adverse effect on the clinical course or prognosis.

This conclusion is valid even if 23 cases with a *P-R* interval of only 0.20 second, usually considered the upper limit of normal, are excluded. However, 0.20 second was probably significant in most of these cases, for the *P-R* interval became shorter at some time in the course of the study. In 31 patients (more than one-half), the *P-R* interval was prolonged to 0.22 second; in 3 to 0.26 second; in 2 to 0.30 to 0.34 second and in 1 to 0.40 second. There were no dropped beats in the latter cases despite the excessive prolongation in *A-V* conduction time.

In three-fifths of the cases the *A-V* conduction disturbance appeared during the first week after the attack (Table 2). In nearly one-third a prolonged *P-R* interval was noted on the first or second day. In almost one-fifth, however, the *P-R* interval did not become prolonged until the third, fourth or even sixth week (Fig. 1). Occasionally a prolonged *P-R* interval, which had become normal early in the attack, reappeared several weeks later without any other change in the clinical condition or in the electrocardiogram of the patient (Fig. 2).

The duration of the *P-R* interval prolongation was more than 1 week in 77% of the 43 cases in which it could be determined (Table 2). It was from 1 to 3 weeks in 6 patients, 1 to 2 months in 11,

* The average number of electrocardiograms taken on each patient was 8. The chest lead shown in the illustrations was taken with the left leg electrode in the left midclavicular line, and the right arm electrode on the left leg, in conformity with the method officially accepted by the American Heart Association (Am. Heart J., **15**, 107, 1938).

3 to 6 months in 9 and was still present after 1 to 2 years in the remaining 7. It appears, then, that *P-R* prolongation may become permanent (Fig. 3), thus differing from other arrhythmias in coronary artery thrombosis which are usually transient.[68a,b]

TABLE 2.—TIME OF ONSET AND DURATION OF HEART BLOCK.

	Prolonged *P-R*.	Partial heart block.	Complete heart block.
Time of onset:			
1–2 days	19	4	4
3–7 days	18	2	1
2–3 weeks	15	0	0
4–6 weeks	7	0	0
Unknown	0	0	1
Duration:			
1–4 days	6	2	3
5–7 days	6	3	0
2–3 weeks	6	0	2
1–2 months	11	0	1
3–6 months	9	0	0
1–2 years	7	1	0

When prolongation of the *P-R* interval persists following coronary artery occlusion, a subsequent attack will often produce a further increase in the conduction disturbance. An instructive illustration of this point is a 50-year-old man whom we observed in three attacks. In the first attack the *P-R* interval measured 0.19 second. After the second it was prolonged to 0.22 second and following the third it increased further to 0.28 second.

Simple *P-R* prolongation was associated with an arrhythmia in only a few patients; 2 developed paroxysmal auricular fibrillation and 1 both paroxysmal auricular tachycardia and ventricular bigeminal rhythm. On the other hand, 16 patients with *P-R* prolongation (26.5%) also had bundle-branch or intraventricular block, an incidence twice as great as in patients with a normal *P-R* interval. Impaired intraventricular conduction was especially common when the *P-R* interval measured more than 0.24 second, being present in 3 of the 6 patients (Fig. 4). This association is emphasized by the case described above, in which both the *P-R* and the *QRS* interval increased progressively after each of three attacks.

An attempt was made to correlate the presence of *P-R* prolongation with the site of infarction (Table 3). In 23 patients it was associated with a *Q*-1 *T*-1 pattern in the electrocardiogram, typical of anterior wall infarction, and in 17 with a *Q*-3 *T*-3 pattern seen in posterior wall infarction. In 10 cases there were signs of both anterior and posterior infarction and in the remaining 10 the changes in the electrocardiogram were atypical. Although, electrocardiographically, anterior infarction seems to be somewhat more frequent than posterior, the small difference does not permit of a definite conclusion. Postmortem examination in 5 of the 8 fatal cases also revealed no specific lesion as a cause for the *P-R* prolongation, both coronary arteries being occluded with equal frequency.

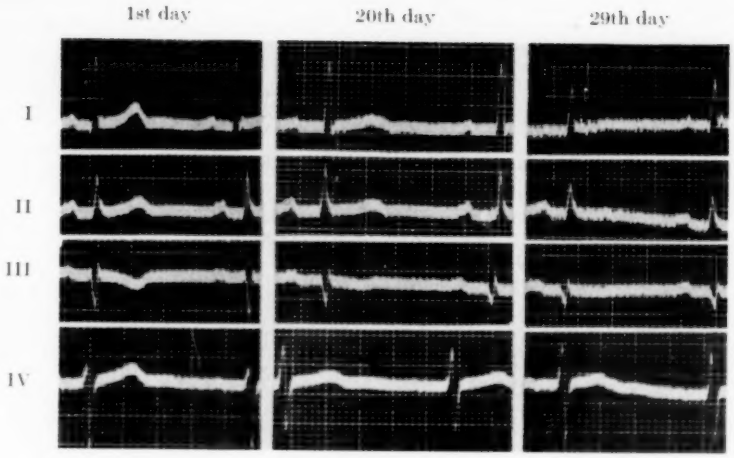

FIG. 1

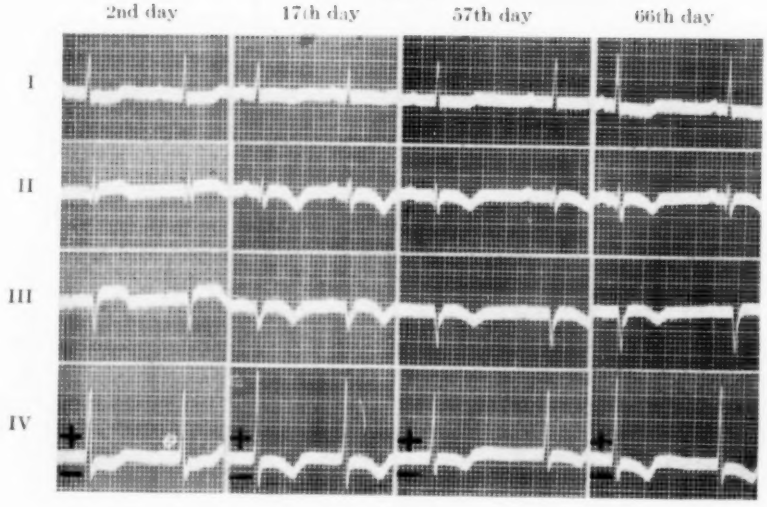

FIG. 2

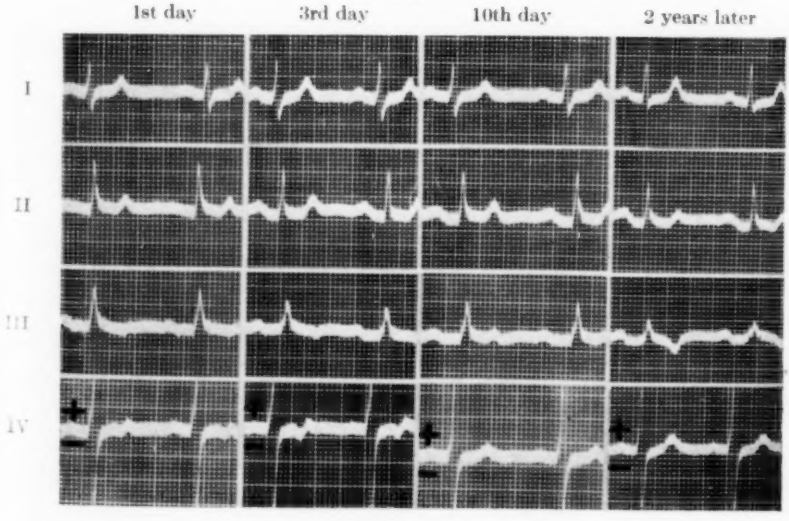

FIG. 3

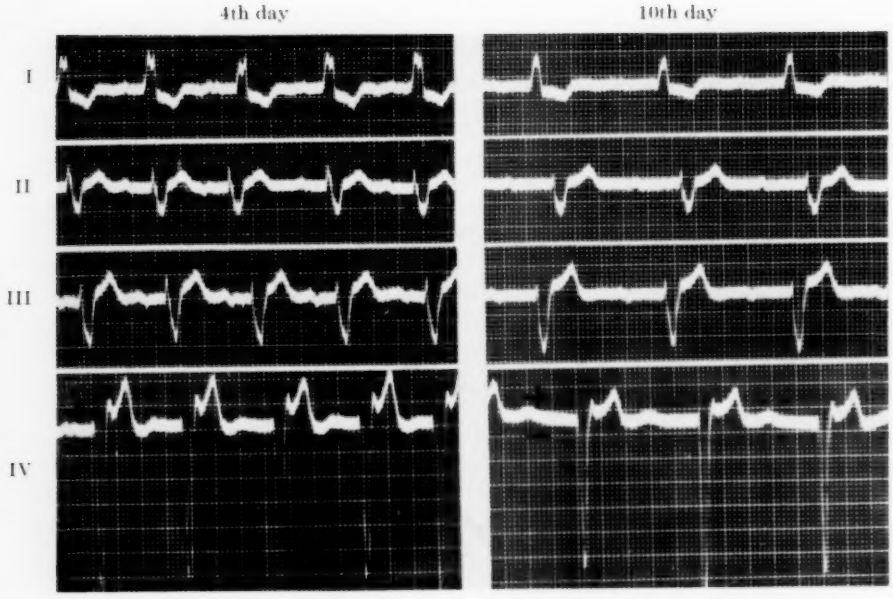

FIG. 4.—Defective *A-V* conduction and left bundle-branch block in acute coronary artery occlusion—male, aged 75. Because of the bundle-branch block the electrocardiogram fails to show characteristic progressive changes of acute infarction. However, the sudden prolongation of the *P–R* interval from 0.26 sec. on the 4th day to 0.40 sec. on the 10th day is diagnostic of acute damage. Necropsy revealed recent and old occlusions of the right coronary artery with infarction and aneurysmal dilatation of posterior wall of left ventricle and septum.

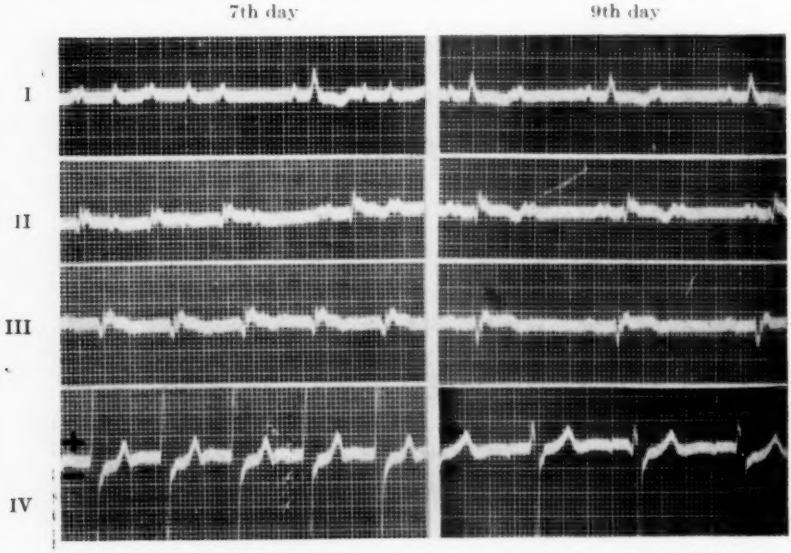

FIG. 5.—Partial heart block in acute coronary occlusion, male, aged 66. Occasional dropped beats and *P–R* interval prolonged to 0.32 sec. on the 7th day. Regular 2:1 *A–V* block on the 9th day, ventricular rate 50. Electrocardiogram characteristic of posterior wall infarction. Death on 10th day.

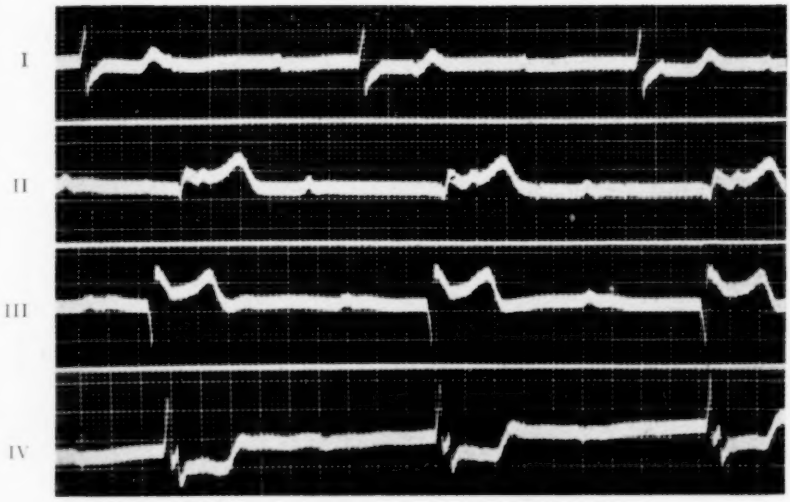

FIG. 6.—Complete heart block in a 70-year-old woman with acute coronary artery occlusion. Typical Q-3 T-3 pattern of posterior wall infarction. Death on 3d day. Necropsy showed recent and old occlusions of right coronary artery with infarction of posterior wall of left and right ventricles and posterior portion of interventricular septum.

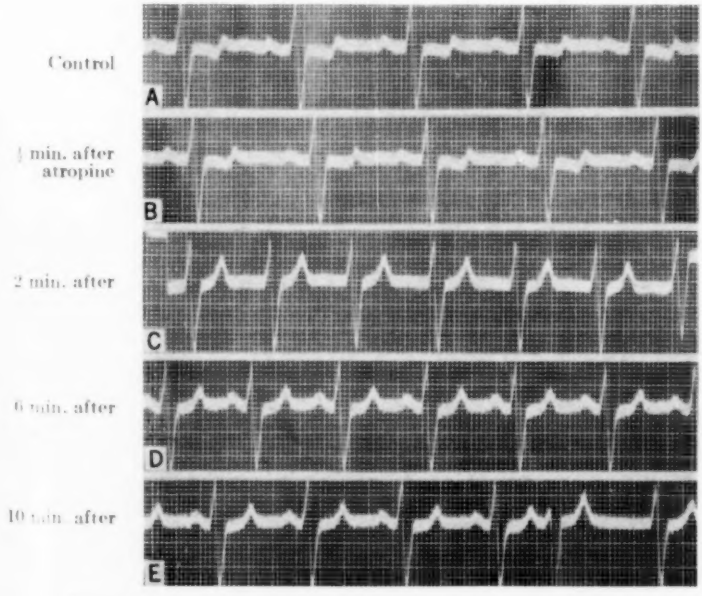

FIG. 7.—Effect of intravenous injection of atropine sulphate, gr. 1/50, on the prolonged P–R interval in acute coronary occlusion. One-half minute after injection the P–R interval has decreased from 0.22 to 0.18 sec. Two minutes later, nodal rhythm, rate 90, appears and persists for several minutes. Six to 10 minutes after injection the P–R interval is still normal, 0.16 sec. The intraventricular conduction defect (QRS 0.15 sec.) is unaffected. This experiment suggests that vagal influences may be responsible in part for prolongation of the A–V conduction time in coronary occlusion.

FIG. 8.—Partial and complete heart block in acute coronary occlusion. Male aged 60. Partial heart block with frequent dropped beats on the 2d day; complete block with ventricular rate of 65 on the 3d day. This persisted until the 8th day, when sinus rhythm, rate 100, returned with a prolonged P–R interval of 0.26 sec. Typical Q–2, Q–3, T–2, T–3 pattern of posterior wall infarction. Necropsy showed recent and old occlusions of right coronary artery with massive infarction of posterior wall of left ventricle and septum.

TABLE 3.—VENTRICULAR RATE. ECG. PATTERN AND ARTERY OCCLUDED.

	Prolonged *P–R*.	Partial heart block.	Complete heart block.
Average ventriculate rate:			
20–40		0	3 (deaths)
40–48		2 (deaths)	0
50–60		2	1
75–100		2	2 (1 death)
ECG. pattern:			
T–1 type	23	1	0
T–3 type	17	5	6
T–1–2–3 type	10	0	0
Atypical	10	0	0
Coronary artery occluded:			
L. A. D.	2	0	0
Right	2	1	4
Left and right	2	0	0

A-V Heart Block. Auriculoventricular block other than simple *P-R* prolongation was present in 12 (3.2%) of the 375 patients (Table 1); partial block with frequent dropped beats in 6 (Fig. 5); complete *A-V* dissociation in 3 (Fig. 6) and both types in the remaining 3 (Fig. 8). Unlike the finding in coronary thrombosis in general, women in this group outnumbered men 2:1. The average age also was higher, 60.5 years as against 56 years in the entire series.

The patients in this group ran a severe clinical course and presented evidence of severe myocardial disease. Heart failure, usually both left and right, was practically universal. Four of the 6 patients with complete block and 1 with partial block had sustained a coronary occlusion in the past (Table 1). Previous hypertension and cardiac enlargement were present in all except 1 case of complete heart block but in only half of those with partial block. Six of the patients died, a mortality rate of 50%. These included 4 patients with complete *A-V* dissociation and 2 with partial heart block.

In 8 of the 12 patients, including 4 with complete block, the block set in on the day of the attack (Table 2); in 2 it began on the third day, in 1 on the fifth and in the remaining case the day of onset could not be determined. Heart block thus occurs very early in coronary occlusion.

The duration of the heart block was variable (Table 2). With partial block, the duration was 2 days in 1 case and less than 1 week in 3; in another case, 2:1 *A-V* block persisted until death 1 year later. In the group with complete heart block, 3 patients died within 2 days following the onset of the attack, the heart block remaining unchanged. In the fourth patient, conduction through the *A-V* system gradually improved so that sinus rhythm with a prolonged *P-R* interval returned on the tenth day (Fig. 8). In spite of this the patient died the following day with increasing heart failure, presumably as a result of very extensive infarction. In the

fifth patient the block lasted at least 2 weeks and in the sixth was intermittent, periods of partial and complete block alternating with periods of normal rhythm for more than a month.

The electrocardiographic findings (Table 3) were of great interest for, with one exception, all the cases of partial or complete block presented the *Q*-3 *T*-3 pattern characteristic of infarction of the posterior surface of the heart following occlusion of the right or left circumflex coronary artery (Figs. 6, 8). The lone exception, a patient with 2:1 heart block, presented the *T*-1 type of electrocardiogram usually seen in occlusion of the left anterior descending artery. Although the patient died of heart failure 1 year later, permission for necropsy was not obtained and we were unable to determine whether there was occlusion of the right coronary artery as well as of the left anterior descending artery.

The postmortem studies corroborated the electrocardiographic findings (Table 3). The 4 fatal cases of complete block and 1 of the 2 fatal cases of partial block were examined; in each there was extensive infarction of the posterior portion of the interventricular septum and posterior surfaces of both ventricles, resulting from occlusion of the right coronary artery. In 2 of these cases the left circumflex artery was also occluded. Only 1 case showed acute occlusion of the left anterior descending artery in addition to the right coronary artery. However, all showed one or more old occlusions of all 3 arteries. It is therefore not surprising that the acute infarction in all the cases was massive and that advanced heart failure existed.

Three of the 5 cases with complete *A-V* dissociation and 1 of those with partial block were further complicated by abnormally wide *QRS* complexes (0.12 to 0.13 second), resulting from an abnormal ventricular focus or impaired intraventricular conduction (Fig. 6). Infarction of the interventricular septum, present at autopsy in all the cases examined, might not only impair conduction through the *A-V* node and main stem of the bundle of His in the upper part of the septum, but might also interfere with conduction through the bundle-branch system in its lower part. The remaining 5 patients with partial block all had *QRS* complexes of normal appearance and duration. It may be that the septal infarction in these cases was not extensive.

Clinical Features. Disturbances in auriculoventricular conduction give rise to symptoms principally when the block is complete and occasionally in partial block with frequent dropped beats. When the blood supply to the *A-V* node or bundle is occluded and auriculoventricular dissociation occurs, there may be sudden cessation of ventricular contraction for a brief period. As a result of the ensuing cerebral anoxemia, the patient may develop syncope or convulsions, *i. e.*, the Stokes-Adams seizure. As the ventricle assumes its own rhythmic contractions and the cerebral flow be-

comes adequate, these symptoms disappear. However, the ventricular rate in complete block is usually between 20 to 40, which is too slow to maintain sufficient blood supply to the brain when associated with the low blood pressure and diminished cardiac output present in coronary artery occlusion. Therefore, when a ventricular rate of 40 or less persists, repeated attacks of syncope or convulsions are apt to occur and the patient not infrequently lapses into unconsciousness or coma. In our cases with complete block the latter type of Stokes-Adams syndrome was the commonest, appearing in all 3 of the 5 cases in which the ventricular rate was 20 to 40 beats per minute. In another patient, periods of complete *A-V* dissociation alternated with intervals of 2:1 block and normal sinus rhythm. During the intervals of block the ventricular rate fell as low as 45 beats per minute and the patient experienced mild syncopal attacks; when the rate rose, these did not occur. In the remaining 2 patients the ventricular rate remained above 75 beats per minute and the block caused no symptoms. In the 6 cases with partial heart block the ventricular rate did not fall below 40; in 2 cases it varied between 75 and 100. Only 1 of these patients presented cerebral symptoms; this was a 70-year-old woman with a 2:1 heart block and a ventricular rate of 50, who was admitted to the hospital in coma, which was attributable not to the slow rate alone but also to the severe degree of shock and congestive heart failure present. It is noteworthy that even this patient survived, although the 3 patients with complete heart block and a rate of 40 or less ended fatally. When *P-R* prolongation was present the heart rate was always above 60 and no cerebral symptoms occurred.

The slow ventricular rate in heart block not only manifests itself by Stokes-Adams seizures but also leads as a rule to severe congestive failure. This is further evidence of the inability of the badly damaged heart to maintain a normal rate of blood flow in the presence of a slow heart rate and low blood pressure.

Except for these manifestations of a slow ventricular rate, *A-V* conduction disturbances give rise to few physical signs other than those usually associated with coronary artery occlusion. When complete *A-V* dissociation is present, the auricular sounds may be distinct, and occasionally the auricular wave is visible in the cervical veins. Partial block with dropped beats produces an irregularity of pulse which may be difficult to differentiate from other arrhythmias such as premature beats or even auricular fibrillation. The diagnosis usually depends on the electrocardiogram and this is also the only means of detecting *P-R* prolongation, since the heart rate is regular and not slow, and there are no signs or symptoms attributable to the mild conduction disturbance.

Syncope and coma produced by heart block in coronary artery occlusion must be differentiated from these conditions as produced by other causes, such as severe shock and cerebral vascular acci-

dents, particularly embolism. We have already pointed out that in coronary artery occlusion with shock, there is a diminution in cardiac output and a marked drop in blood pressure which may result in cerebral anemia, and consequently, syncope or coma, even with a normal heart rate. It is noteworthy that these conditions obtain early in the attack when heart block also is apt to occur, and when syncope is present both causes should be considered.[61] Clinical observation of the pulse will usually determine the diagnosis; if it is slow, *i. e.*, 40 beats per minute or less, complete heart block is probably present. It must be remembered, however, that cerebral disturbances alone may also result in reflex slowing of the heart rate; therefore it may be necessary to rule out heart block by the electrocardiogram. Embolism to the brain from intramural thrombosis may give rise to cerebral symptoms identical to those of heart block but this usually occurs later in the course of the attack and the heart rate is not slowed.

The sudden appearance of auriculoventricular block may be, as in other arrhythmias, the first, and occasionally the only, indication of occlusion of a coronary artery, as Levine and Tranter[62] emphasized. It is important to consider the possibility of coronary occlusion in the presence of a sudden onset of heart block. This is particularly true when the block is accompanied by the Stokes-Adams syndrome which may completely mask the other features of the occlusion, such as pain.

Simple prolongation of the *P-R* interval may be of great diagnostic significance since it is occasionally the only electrocardiographic abnormality (Fig. 1). A case in point is that of a 50-year-old man who was admitted to the hospital following a prolonged attack of precordial pain. Although typical clinical signs of coronary artery occlusion were present, including a drop in blood pressure, fever and leukocytosis, repeated electrocardiograms failed to show any change until 3 weeks after the attack, when the *P-R* interval became lengthened to 0.24 second. This case also illustrates the necessity of taking records persistently in coronary artery occlusion, for not only may a prolongation of the *P-R* interval be the only change in

LEGENDS FOR FIGS. 1, 2 AND 3.

FIG. 1.—Acute coronary occlusion with normal electrocardiogram except for prolongation of the *P–R* interval. On the 1st day the *P–R* is 0.20 sec. It suddenly becomes prolonged to 0.24 sec. on the 20th day. On the 29th day it is again 0.20 sec.

FIG. 2.—Prolonged *P–R* interval following acute coronary occlusion in a 60-year-old woman. *Q–3 T–3* type of electrocardiogram. The *P–R* interval is prolonged to 0.22 sec. on the 2d day; normal on the 17th day (0.14 sec.); prolonged temporarily on the 51st day (0.22 sec.), without any other clinical or electrocardiographic change.

FIG. 3.—Permanently prolonged *P–R* interval in a 50-year-old woman with acute coronary occlusion. Progressive prolongation of the *P–R* interval from 0.22 sec. on the 1st day to 0.24 sec. on the 3d day, and to 0.26 sec. on the 10th day. The *P–R* prolongation became permanent, being present after 2 years.

the electrocardiogram, but it may not appear for some time after the attack. Furthermore, when *P-R* prolongation is associated with *T*-wave abnormalities these may remain fixed and the *P-R* interval alone show changes in serial records.

It is interesting to speculate on the relation of coronary artery occlusion to chronic complete heart block or prolonged *P-R* interval. It is probable that in many instances these have been initiated by an occlusion. We have seen that prolongation of the *P-R* interval may persist for months or years after an occlusion and White and his coworkers[35,81] found that 10 to 12% of 190 cases of chronic heart block had followed a coronary occlusion. Furthermore, anatomic studies in some cases of chronic complete heart block have shown complete occlusion of the arteries supplying the interventricular septum. Postmortem studies have taught us that coronary occlusion is more frequent than has been suspected since it may occur without producing any characteristic history or clinical evidence of the disease.

Smith[90] stated that coronary artery occlusion rarely occurs in the presence of complete *A-V* dissociation. He cited one exception and Lyon[66] has observed another. Also 1 of our patients gave a history of syncope before the attack, suggesting the existence of complete heart block.

Pathogenesis. Our cases of complete and partial heart block, as well as the majority of those cited by others, exhibited at necropsy occlusion of the right coronary artery with infarction of the posterior surface of both ventricles and the posterior portion of the interventricular septum. Occasionally only the left circumflex coronary artery has been found occluded, but this too resulted in posterior wall infarction. That the latter was present in the cases not examined pathologically was evidenced by the presence of the characteristic *Q*-3 *T*-3 pattern in the electrocardiogram. These findings can be readily explained anatomically, since auriculoventricular block results from disturbed conduction through the *A-V* node or bundle of His, which are situated in the upper posterior part of the interventricular septum. In 92% of hearts the blood supply to this region is derived from the right coronary artery through the ramus septi fibrosi, the specific artery to the *A-V* node.[37,67] Sudden occlusion of the right coronary artery above the origin of this branch, or of the specific artery itself, may result in infarction of the upper posterior part of the septum and lead to delay or complete interruption in the passage of the impulse from auricles to ventricles.

One might therefore anticipate some degree of block in all or in the majority of cases in which the right coronary artery is occluded, and since right coronary artery occlusion is as frequent as that of the left coronary artery,[6,68d,87] heart block should be a common finding. Yet we have seen that it occurs in not more than 5% of cases. There are several reasons for this discrepancy, the most important being

the presence of profuse anastomotic channels between the left and right coronary arteries in the region of the *A-V* node and bundle of His in the upper part of the septum, particularly the arteria anastomotica auricularis magna.[17,37,38,51,58] Stenosis of the specific artery to the *A-V* node has been observed[17,51] without clinical or electrocardiographic evidence of any lesion. The collateral circulation is important not only in preventing the onset of heart block, but also in effecting its remission once it has set in. Another explanation of the fact that heart block is not more common in coronary thrombosis lies in the high origin of the ramus septi fibrosi. It has been emphasized by Smith,[90] Ball[4] and Wilson[100] that this vessel leaves the right coronary artery proximal to the usual site of thrombosis, so that the circulation to the junctional tissues is rarely compromised.

Although heart block is associated as a rule with occlusion of the right coronary artery, occasionally it follows closure of the left, as illustrated by an electrocardiogram of the *T*-1 type in one of our cases, and in one published case.[39] Furthermore, postmortem examination in several cases[3,15,74,88,99,100] revealed thrombosis of the left anterior descending artery with infarction of the upper part of the interventricular septum. That occasional cases of this kind occur is not surprising since we have seen that in 8% of cases the *A-V* node is supplied by the left coronary artery. Furthermore, if there is preëxisting stenosis of the right coronary artery, sudden occlusion of the left may result in heart block because the collateral circulation to the posterior septum has been cut off.

Rarely heart block has been described in the presence of an intact *A-V* node and bundle.[31,33,75] This was attributed to anoxemia resulting from diminished blood flow. The *A-V* node has been found markedly sensitive to anoxemia.[18,19,80] Since shock and heart failure are severest within the first few days following the occlusion, anoxemia of the myocardium is greatest during this time and this predisposes to the early appearance of heart block observed in most cases.

The mechanism of the production of heart block thus far discussed is the one generally accepted, but other explanations have been offered. The chief of these is that the block in conduction does not occur in the *A-V* node or main stem of the bundle of His but in the lower part of the interventricular septum where the infarction compromises conduction through both bundle-branches. Several authors[15,39,67,102] have observed cases of coronary thrombosis in which evidence of bundle-branch block recorded in the electrocardiogram preceded the appearance of heart block. It was thought that the infarction in the septum at first involved one bundle-branch causing bundle-branch block and then the other, producing complete *A-V* heart block.

Although Ball[4] stated that in complete block the *QRS* complex was

always supraventricular in type, in 3 of our 6 cases with this arrhythmia it measured 0.12 to 0.13 second. Similarly 13 of the 15 cases reported by Schwartz[87] presented intraventricular block. This suggests that there was simultaneous block in conduction through the bundle of His and one or both of its branches. It is interesting to repeat that the septum in our 3 cases showed very extensive infarction, both in its upper and lower portions.

Unlike the severer grades of block, the electrocardiographic and pathologic changes in *P-R* prolongation were not uniform. The septum was involved in only 3 of the 5 cases. It is probable, therefore, that other factors, in addition to the injury to the *A-V* node, come into play in the production of *P-R* prolongation. The most important of these is doubtless anoxemia to which the *A-V* node and junctional tissues are highly sensitive.[19,80] Asphyxiation in cats is followed by increasing *A-V* block;[63] in dogs and men anoxemia causes a progressive delay in auriculoventricular conduction ending in complete block.[36] Clinically, it is known that heart block may occasionally appear during heart failure and disappear after treatment.[5] Because of the coronary insufficiency and heart failure present in our patients, it is not surprising that so many of them showed a mild decrease in *A-V* conduction time up to 0.24 second. On the other hand, since anoxemia is most severe at the onset of an attack, it is difficult to explain on this basis the facts that *P-R* prolongation may appear for the first time several weeks after an occlusion and that it may persist for long periods, even permanently.

That the vagus nerve, in combination with anoxemia, may be important in the production of *P-R* prolongation is illustrated by the experiments of Greene and Gilbert.[36] After producing impaired *A-V* conduction in dogs following rebreathing of air with reduced oxygen tension, they were able to abolish it by cutting the vagi. We have not been able to determine whether simple prolongation in coronary thrombosis is also associated with increased vagal influence. If this is true, atropine should abolish the conduction disturbance. Administration of this drug in 3 of our cases indicates that vagal influences probably play a rôle in the depression of auriculoventricular conduction in coronary artery occlusion, but its importance should be evaluated by further study. In 1 case in which atropine gr. $\frac{1}{75}$ was injected intravenously, the *P-R* interval, which measured 0.24 to 0.28 second became more prolonged and 2:1 partial block promptly developed. This result is not so unusual as it appears to be, for the auricular rate was increased from 75 to 100 and with a damaged conduction system this rise in rate was sufficient to increase the degree of block by reducing the diastolic interval and the recovery period of the *A-V* node. In a second case, atropine gr. $\frac{1}{30}$ intravenously reduced a *P-R* interval of 0.22 to 0.24 second to 0.16 second within a few seconds, following which the sinus rhythm was replaced by nodal rhythm (Fig. 7). In a third

case, a similar dose of atropine reduced the *P-R* interval from 0.22 to 0.18 second.

Prognosis. Although patients with complete heart block in coronary artery occlusion may recover and several authors[3,55,87] have offered a not unfavorable prognosis, this arrhythmia usually portends a fatal issue.[22,54] In our series 4 of the 6 patients died, a mortality rate of 66.7%. But this result is not surprising when we recall that their average age was higher than that of patients without heart block, the degree of cardiac enlargement and heart failure greater and very extensive infarction usually present. In a previous investigation,[68a] we found each of these factors associated with a rise in mortality rate.

The most significant factor leading to death in these cases of complete block complicating coronary occlusion is the slow rate of the heart which is usually under 40 beats per minute. The marked bradycardia reduces the blood flow and seriously interferes with the already disturbed nutrition of the heart, as well as other organs, an effect enhanced by the lowering of blood pressure which occurs following coronary occlusion. That patients with chronic complete block are often able to maintain adequate circulation for many years is due to the fact that there is present a compensatory increase in systolic blood pressure which is frequently 200 mm. or more. However, such a compensatory mechanism cannot develop for some time after an infarction, and the unfavorable effect of bradycardia predominates. The majority of cases of complete block described by other authors in which the rate was 40 or less also proved fatal. In the 2 cases in our series which survived, the rate was 75.

The prognosis in partial heart block with dropped beats is usually favorable,[54,61] but also depends on the ventricular rate. Two of our 6 cases died and in both the rate was 40 to 48 beats per minute. In those who survived it was 50 to 100.

Simple prolongation of the *P-R* interval was of no prognostic significance since it did not affect the clinical course or mortality rate.

Therapy. Complete heart block, because of the marked bradycardia which it usually produces, may lead to the Stokes-Adams syndrome and, as we have seen, is very often fatal. Since an increase in the heart rate may lead to recovery, treatment to this end should be instituted in cases with rates below 40 and Stokes-Adams seizures; when there are no symptoms of inadequate circulation such treatment is unnecessary. Levine[61] and Schwartz[87] have advocated the use of adrenalin for the Stokes-Adams syndrome and Schwartz particularly has had satisfactory results in increasing the ventricular rate or temporarily restoring normal rhythm. However, because of the danger of adrenalin in coronary artery disease, especially thrombosis, the drug must be used cautiously. Since the action of ephedrine is similar to that of adrenalin, the same care must be observed

in its use. During a period of syncopal attacks Schwartz[87] gave repeated intramuscular injections of adrenalin hydrochloride in doses of 1 cc. of a 1:1000 solution, until normal rhythm returned or the ventricular rate became fixed. Then ephedrine sulphate in 30 mg. doses orally was substituted and given 3 or 4 times a day.

Partial heart block usually produces no symptoms and needs no specific treatment. In those cases in which it causes marked slowing of the ventricular rate and cerebral symptoms, the treatment is similar to that for complete heart block. No therapy is required for simple prolongation of the *P-R* interval.

Atropine has occasionally been used with success in cases with disturbance in auriculoventricular conduction, caused presumably by increased vagal tone. Observers have pointed out that this drug shortens the prolonged *P-R* interval in pneumonia[70] and in rheumatic fever.[16] We have already discussed its intravenous use in 3 of our cases of coronary occlusion with *P-R* prolongation. In 2 it improved auriculoventricular conduction but in the third it precipitated 2:1 heart block by increasing the auricular rate. Since simple *P-R* prolongation does not add to the gravity of the prognosis in coronary artery occlusion no treatment is required for it. In partial heart block with a slow pulse atropine may be administered in the hope that it will improve auriculoventricular conduction without increasing the auricular rate. In 2 of the cases of complete heart block reported by Schwartz[87] the injection of atropine produced a rise in ventricular rate, but this was only transitory. In a case of ventricular tachycardia in coronary occlusion reported by Salley,[82] atropine caused a slowing of the ventricular rate from 115 to 30, with persistent complete *A-V* dissociation. Wedd[97] reported a case of coronary artery occlusion with complete heart block in which the latter disappeared 4 to 6 minutes following the injection of atropine but was succeeded by 2:1 heart block. In spite of these poor results the effect of atropine should be studied further.

An attempt to increase the heart rate with adrenalin or atropine was made without success in 4 patients of our series, 2 with complete, and 2 with partial, heart block. In the first case, complete block with a ventricular rate of 30 to 40 and coma, several injections of adrenalin were given. In the second, repeated episodes of complete and incomplete block alternated with sinus rhythm, and atropine and ephedrine were given orally in large doses. In the cases with partial block, atropine and adrenalin were administered.

The general treatment of coronary artery thrombosis we have described in several reports.[68c,69a,b] In summary, its purpose is to reduce the work of the heart by restricting the diet and providing complete rest in bed, employing morphine or other sedatives liberally if necessary. For some days after the attack the diet consists of small meals totalling a few hundred calories daily. This regime lowers the basal and total metabolism of the body and therefore the

work of the heart, and in addition, minimizes gastrocardiac reflexes. As the patient improves the diet is increased to 800 calories, which is continued for 2 to 4 weeks, depending on the condition of the patient. Often the patient feels well and no treatment is required other than rest in bed for from 4 to 6 weeks.

Very frequently coronary artery occlusion is followed by some degree of heart failure, which increases in spite of bed rest and restriction of fluids and salt intake. When this occurs we have found that diuretics, such as mercupurin, give very satisfactory results, and should be employed first. Oxygen is useful when there is obvious cyanosis or dyspnea. Occasionally venesection must be resorted to, particularly when pulmonary edema is present. These measures may relieve not only the heart failure but also the disturbance in auriculoventricular conduction, in the occurrence of which the anoxemia of heart failure may play a rôle.[5] As the failure disappears the circulation to the septum and conduction through it improve.

We avoid the use of digitalis after coronary occlusion since it increases the work of the heart,[92] an undesirable effect after an attack. In addition, it may initiate an arrhythmia,[68b] such as ventricular tachycardia or auricular fibrillation. We have shown that ventricular tachycardia is rare in coronary artery occlusion; its occurrence has usually followed the use of digitalis. When *A-V* conduction is impaired the drug may be even more dangerous, since it depresses *A-V* conduction. Partial block, or if this is already present, complete block may be produced and an innocuous arrhythmia converted into a very serious one. Since mercurial diuretics, *e. g.*, mercupurin, are efficient in the treatment of heart failure, we believe it permissible to use digitalis only when these have failed or after the acute stage of the attack has subsided.

Quinidine, too, in our opinion is a dangerous drug to use in coronary artery occlusion. It may increase the *A-V* conduction[34,64] time, as evidenced by prolongation of the *P-R* interval. Like digitalis, therefore, it is especially undesirable when some degree of heart block already exists and its use should be limited to cases with persistent ventricular tachycardia.

Summary. 1. A complete review has been made of the *A–V* conduction disturbances in 375 cases of coronary artery occlusion with reference to their incidence, clinical, electrocardiographic and pathologic features, prognosis and treatment.

2. Simple *P-R* prolongation was common, occurring in 16% of cases; partial and complete heart block occurred in 3.2%.

3. Heart block appeared soon after the onset of the occlusion and usually lasted 1 to 2 weeks. *P-R* prolongation not infrequently appeared late and became permanent.

4. Permanent *P-R* prolongation and heart block may be the result of previous unrecognized coronary occlusion. Repeated

attacks of occlusion may progressively increase the *A-V* conduction defect.

5. The sudden onset of *P-R* prolongation as well as heart block may be the first and only sign of coronary artery occlusion.

6. Heart block, excluding *P-R* prolongation, was associated with heart failure, cardiac enlargement, previous hypertension and previous coronary occlusion. It was more common in older patients with advanced arteriosclerosis.

7. Symptoms attributable to the heart block appeared only when the ventricular rate fell to 40 or less, and consisted of heart failure or the Stokes-Adams syndrome with syncope and coma. The bradycardia can differentiate the latter from syncope and coma due to other causes, such as shock and cerebral embolus.

8. The prognosis of complete heart block was serious, because of the slow ventricular rate. Four of the 6 patients died. Partial heart block offered a favorable prognosis unless there was marked bradycardia. Simple *P-R* prolongation did not affect the outcome of an attack adversely.

9. It was confirmed that complete and partial heart block were associated with a specific cardiac lesion and electrocardiographic pattern. The anatomic basis was infarction of the posterior portion of the interventricular septum and posterior surface of the left ventricle as a result of right coronary artery occlusion. The electrocardiogram presented the *Q-3 T-3* pattern typical of posterior wall infarction.

10. The presence of profuse anastomotic channels in the interventricular septum around the *A-V* node prevents the more frequent occurrence of heart block and effects its remission when it does occur.

11. *P-R* prolongation was not associated with a specific anatomic lesion or electrocardiographic pattern. Anoxemia, heart failure, and vagal influences were probably significant.

12. The association of *A-V* block with intraventricular block can be attributed to septal infarction which involves simultaneously the *A-V* tissues and bundle-branch system.

13. The treatment of heart block is that of coronary artery occlusion in general. When there are persistent bradycardia and Stokes-Adams manifestations, adrenalin should be resorted to. The indications and effects of adrenalin, ephedrine and atropine are discussed. Digitalis, quinidine and nitroglycerine were considered contraindicated.

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KIDNEY FUNCTION AND UREMIA IN RENAL AMYLOIDOSIS.

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For many years it was believed that renal amyloidosis was not associated with renal insufficiency and that uremia occurring in the course of the disease was a rarity. The term amyloid nephrosis, applied to the condition by Fahr, has served to convey the impression that the course of amyloid disease of the kidney was similar to that of lipoid nephrosis, and, therefore, that azotemia was not to be expected. In recent years, however, cases of renal amyloidosis terminating in uremia have been reported with increasing frequency. Thus Dixon[6] noted azotemia in 12 of 100 cases, Bell[2] in 11 of 65 cases, and Rosenblatt[14b] in 8 of 87 cases. Other reports of uremia in amyloidosis have appeared in the literature by the following: Noble and Major (3 cases),[13] Zadek (3),[18] Jennings, Altnow and Higgins (1),[8] Carey (1),[5] Bannick and Barker (1),[1] Linder, Maxwell and Green (1)[9] and others.

On our metabolic service we have opportunity to observe a considerable number of patients with amyloidosis, and it has, for some time, been our impression that impairment of renal function usually developed in renal amyloidosis that had existed for some time. It was believed that a review of the cases would serve to confirm or disprove this opinion.

In the present article, the cases of renal amyloidosis that either died or left this hospital between January 1, 1935, and August 1, 1937, are reviewed.

Since the introduction of the Congo Red test in 1923 by Bennhold,[3] and the more recent clinical-pathologic evaluation of the test by Lipstein and Auerbach,[11] and by Lipstein,[10] the diagnosis of amyloidosis has become relatively simple and accurate. Bennhold originally stated that an absorption of 60% or over of the dye indicated the presence of amyloid disease. Lipstein and Auerbach, however, after correlating the Congo Red absorption during life with the autopsy findings, concluded that an absorption of 90% or more of the dye was necessary to establish the diagnosis of amyloid disease.

In this study, the following criteria are used for the diagnosis of renal amyloidosis: 1, evidence of a predisposing primary disease; 2, albuminuria; and 3, a Congo Red test with an absorption of 90% or more of the dye. Occasionally amyloidosis has been reported when no predisposing illness could be found, but such cases are extremely rare. Corroborative findings of an enlarged liver or spleen, and of edema, are valuable in arriving at the diagnosis, but are, in our experience, not essential. It is common to find amyloid involvement of the liver and spleen at autopsy when these organs are not palpable during life. Cases of amyloidosis have been reported in which the kidneys alone were affected (Rosenblatt,[14] Bell[2]).

The primary disease in all of the present cases was tuberculosis of either the lungs or bone. This is to be expected, since this hospital is a tuberculosis institution. However, even in general hospitals, tuberculosis is by far the most frequent predisposing illness; it was the primary disease in 82% of Saleeby's[15] 50 cases from the Philadelphia General Hospital and in 110 of 125 cases reviewed by Rosenblatt[14] at the Montefiore Hospital.

Albuminuria must be present in considerable amounts to warrant a diagnosis of amyloid disease of the kidney, and, in the selection of our cases, we included only those in which there was + + albumin or more in the urine. Waldenström[17] points out that even extensive amyloidosis may be present without albuminuria, but this, according to our experience, is extremely rare. It is impossible clinically to make a diagnosis of renal amyloidosis without the presence of albuminuria. The appearance of only a trace of albumin in the urine cannot be considered significant, since many tuberculous patients with this finding do not have amyloid disease at autopsy.

Of the patients that either died or left the hospital between January 1, 1935, and August 1, 1937, there were 189 in whom a diagnosis of amyloidosis had been made. Of this group, using the criteria previously outlined, there were 93 that could be classified as cases of renal amyloidosis. Several other cases were excluded

because, although they presented the findings of amyloid disease of the kidney, there was evidence of some other complication such as renal tuberculosis which might interfere with an accurate interpretation of the renal function. Thirty-one of the 93 patients came to autopsy and in each instance the postmortem findings confirmed the antemortem diagnosis.

TABLE 1.—RESULTS OF 2-HOUR TEST FOR RENAL FUNCTION.

No. of cases.	Maximum sp. gr. of urine.	% of cases.
8	1.024 or higher	21.0
3	1.021 to 1.023	7.8
4	1.018 to 1.020	10.5
6	1.015 to 1.017	15.8
6	1.012 to 1.014	15.8
11	1.011 or lower	29.0
Total, 38		

Tests with a maximal specific gravity of less than 1.018 were considered to indicate impairment of renal function.

Two-hour tests for renal function were made in 38 of the 93 patients at some time during the course of their renal amyloidosis (Table 1). From this table it is seen that in 23 of these 38 patients the maximum specific gravity of the urine was under 1.018. If we consider that the normally functioning kidney should excrete urine with a specific gravity of 1.018 or higher, then 60% of these 38 patients showed evidence of impaired renal function. It should be kept in mind that in a number of these patients the renal concentration test had been carried out shortly after evidence of renal involvement had appeared, and thus it is quite probable that had the urinary concentration been determined at a later date, the percentage of cases showing impairment would have been higher.

The non-protein nitrogen of the blood was estimated in 67 of the 93 cases after evidence of renal amyloidosis had appeared. In 12 patients the N.P.N. ranged between 25 and 30 mg.%; in 20 it was 30 to 35 mg.%; and in 15 it ranged between 35 and 45 mg.%. There were 20 patients (Table 3) in whom the blood N.P.N. was above 45 mg.%. In many of the cases several blood chemistry determinations had been performed at varying intervals after the diagnosis of amyloid disease of the kidney had been made, but for the tabulations, only the last N.P.N. determination is recorded. A non-protein nitrogen of 45 mg.% or higher was regarded as definite evidence of azotemia. Twenty of the 67 cases (29.8%) showed unequivocal evidence of renal insufficiency. Eleven of these 20 patients died of uremia; the remaining 9 died of the primary disease or of complications of the primary disease before uremia had set in.

An attempt was made to correlate the duration of the renal amyloidosis and the advent of azotemia in order to ascertain whether there is a tendency, in amyloid disease of the kidney, towards progressive renal insufficiency and ultimate uremia. If the supposition

is correct that amyloid degeneration of the kidney is usually associated with an advancing impairment of renal function, then the incidence of azotemia should be in direct proportion to the length of survival after the appearance of renal amyloidosis. Consequently, the 93 cases of renal amyloidosis were divided into two groups—those that were not associated with azotemia and those that were. The cases of doubtful duration of the amyloid disease were excluded from each group. These doubtful cases included patients that left the hospital and those that showed evidence of renal amyloidosis at the time of admission so that it was impossible to determine the approximate duration of the disease. Only those cases in which the signs of amyloid disease of the kidney developed during their stay in the hospital were included.

The onset of renal amyloidosis was determined by the time at which albuminuria first appeared. This probably does not represent the actual onset of the disease since at autopsy minimal deposits of amyloid in the kidney frequently occurred when there had been no albuminuria during life. However, from a clinical point of view, the time of the appearance of albuminuria represents the closest possible approximation of the onset.

In the non-azotemic group there were 73 patients. Of these, 25 were considered to have renal amyloidosis of doubtful duration and were therefore excluded. In Table 2 are grouped the remaining 47 cases according to the duration of the amyloid disease. These patients all died of the primary disease or of complications of the primary disease. The patients who had developed renal insufficiency and died either of the primary disease before the stage of uremia had been reached or who died of uremia are also analyzed in Table 2. There was a total number of 20 cases in this group. Of these, 4 cases were excluded because of doubtful duration of the renal amyloidosis.

TABLE 2.—COMPARISON OF DURATION OF LIFE BETWEEN THE NON-AZOTEMIC CASES OF RENAL AMYLOIDOSIS AND THE AZOTEMIC CASES.

Duration of renal amyloidosis (yrs.).	Non-azotemic cases.		Azotemic cases.	
	No. of cases.	% of cases.	No. of cases.	% of cases.
Less than ½	29	61.7	6	37.5
½ to 1	11	23.4	3	18.7
1 to 1½	4	8.5	2	12.5
1½ to 2	1	2.1	2	12.5
2 to 2½	1	2.1	1	6.2
2½ to 3	0	0	0	0
3 to 3½	0	0	2	12.5
3½ to 4	1	2.1	0	0
Total	47	..	16	..

The non-azotemic cases are those dying as the result of the primary disease and not because of kidney involvement; the azotemic cases are those which exhibited renal insufficiency. As a group the azotemic cases lived longer than the non-azotemic. The inference is made that all the cases would have become azotemic, and died of uremia, if the primary disease had not been the cause of an early death.

A comparison of the two groups shows that the duration of the amyloid process was usually longer in those patients who had azotemia. Only 14.8% of the non-azotemic cases lived more than 1 year, while of those with an elevated blood N.P.N., 43.7% lived more than 1 year.

In 4 of the 7 patients in the non-azotemic group that lived more than 1 year, renal function tests were carried out at intervals of several months after the onset of the disease. The results of these tests indicated a progressive impairment of renal function in each instance, and before death the maximum specific gravity of the

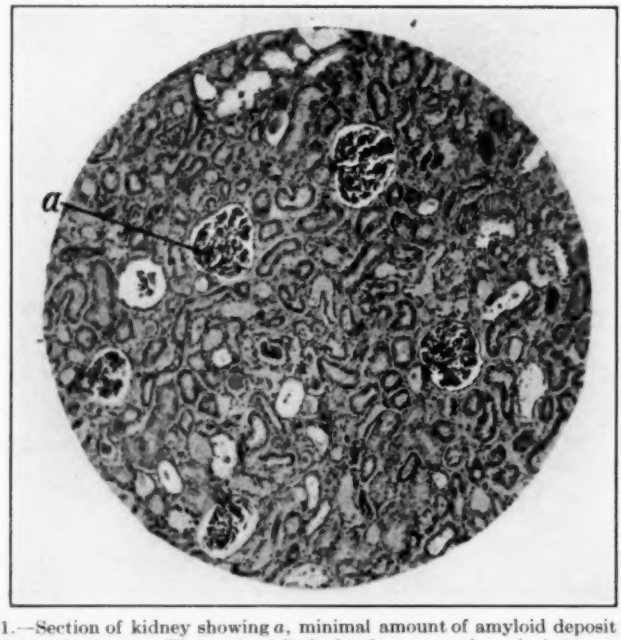

FIG. 1.—Section of kidney showing *a*, minimal amount of amyloid deposit in some of the glomerular loops. The patient died of pulmonary tuberculosis 1 month after the appearance of albuminuria.

urine was below 1.018 in all. From these results it appears that the amyloid deposition in the kidney is persistently progressive and had these patients lived longer, they would have developed azotemia.

These facts suggest that impairment of renal function advances constantly in amyloid disease of the kidney, and that the longer the individual lives, the more likely is the development of marked renal insufficiency. It is to be noted, however, that in some cases renal insufficiency manifests itself rather rapidly and in others more slowly. It is only natural to expect that the rate of amyloid deposition must vary in individual cases, probably depending upon the severity of the primary disease.

Unlike most renal conditions in which a progressive renal insufficiency occurs, amyloid disease of the kidney is usually associated with a normal or low blood pressure. The blood pressure readings in the 20 cases in which azotemia was present are recorded in Table 3. Only 3 of these patients (Cases 13, 15, and 20) can be regarded as having developed hypertension and in 2 the blood pressure was only slightly elevated. Thus it is evident that even in the presence of progressive renal insufficiency and uremia, the blood pressure in the large majority of cases remains normal or low. This finding is

FIG. 2.—Section of kidney showing deposition of amyloid substance in most of the glomeruli *a*, *b*. Note that the amyloid involvement is more extensive than in Fig. 1. This patient died of pulmonary tuberculosis 3 months after albuminuria developed.

in agreement with that of most authors (Bell,[2] Dixon,[6] Rosenblatt,[14] Moschcowitz[12]). There have been occasional reports of hypertension in cases of renal amyloidosis terminating in uremia (Jennings *et al.*,[8] Noble and Major,[13] Bell,[2] and Fahr[7b]). It is interesting to note that in most of the cases recorded in which hypertension was present, contracted kidneys were found at autopsy, whereas in those patients that died of uremia associated with a normal blood pressure, the usual necropsy finding was the large, smooth, pale, waxy kidney.

Of the 3 patients in whom hypertension was noted, an autopsy

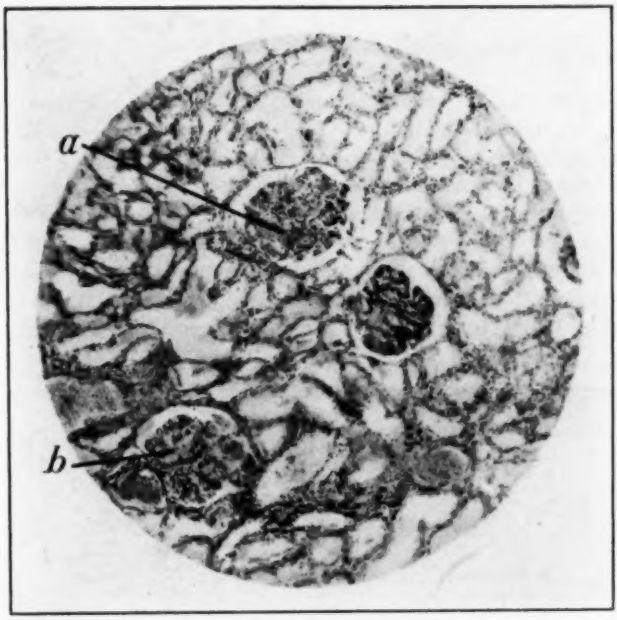

FIG. 3.—Section of kidney in which there was amyloid involvement of most of the loops of nearly all glomeruli *a*, *b*. The amyloidosis is more extensive in this case than in the preceding 2. The patient died of pulmonary tuberculosis 18 months after the diagnosis of renal amyloidosis was made. There was impairment of renal function as determined by the renal concentration test, but no azotemia.

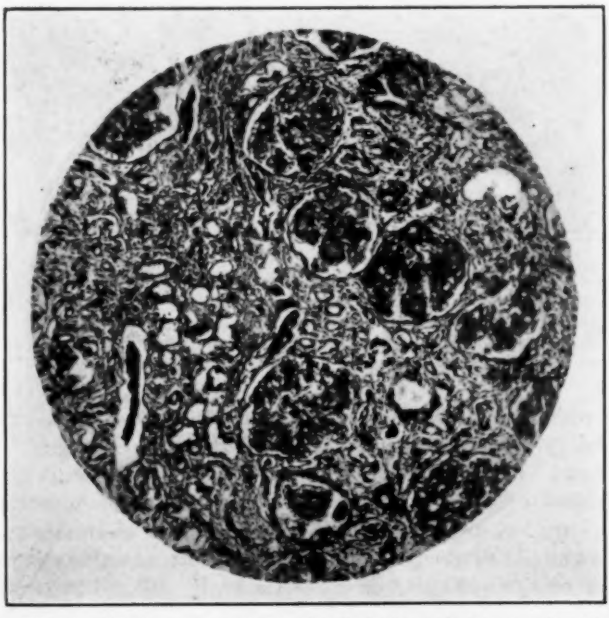

FIG. 4.—Section of kidney of a patient who died of uremia 2 years after the appearance of albuminuria. Note the extensive amyloid deposit in the glomeruli and the paucity of blood cells in the glomerular loops. There was tubular atrophy and increased interstitial fibrosis. The kidneys grossly were large, pale, smooth and waxy.

was performed on 1 (Case 20) and in this instance contracted amyloid kidneys were found.

The low blood pressure associated with amyloid disease of the kidney cannot be attributed to cachexia as Fahr[7b] believes. In the study of our cases, blood pressure determinations had been made, in most of them, at frequent intervals throughout the course of the disease and the pressure remained consistently low in all except those recorded with hypertension. Although cachexia is marked in most patients terminally, the general condition remains fairly

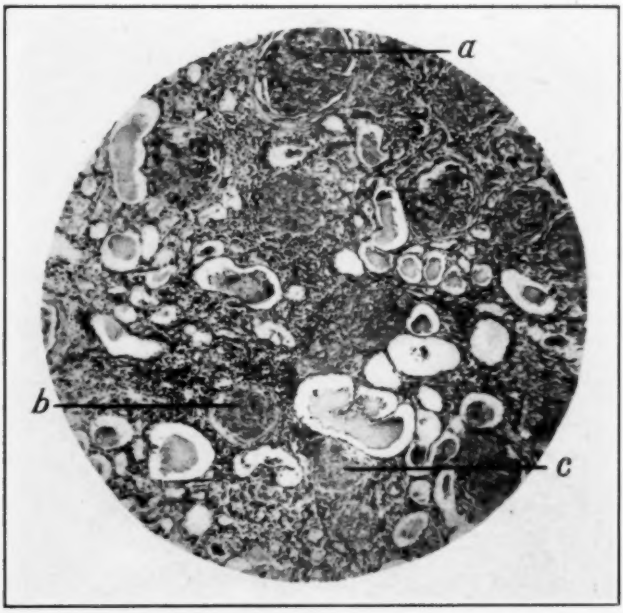

FIG. 5.—Section of kidney from a patient who died of uremia 3½ years after the clinical onset of renal amyloidosis. At autopsy, amyloid contracted kidneys were found. Note the extensive involvement of the glomeruli and the marked tubular atrophy and interstitial fibrosis. At *a* is seen a glomerulus in which there is extensive amyloid deposition. At *b* the amyloid is being replaced by hyaline connective tissue and at *c* the amyloid has been completely replaced by fibrous tissue.

good in many until shortly before death. Nor can the normal or low blood pressure be entirely attributed to the etiologic tuberculous disease. On our wards there are patients with either essential hypertension, or chronic glomerulonephritis in whom severe hypertension is present in spite of the associated tuberculous disease.

In 9 of the patients with renal insufficiency that came to autopsy, the heart was found enlarged in 3 (Cases 10, 19 and 20). In 1 of these (Case 10) mitral stenosis was found, so that the enlargement in this instance cannot be attributed to a preceding hypertension.

Of the remaining 2 cases, 1 (Case 20) had had clinical hypertension and the other (Case 19) a normal blood pressure.

The eyegrounds in renal amyloidosis with azotemia have been observed to be normal by most investigators and we have been able to corroborate that finding. This also indicates that hypertension had not existed. The eyegrounds were examined in 7 patients with uremia and in none of these were abnormal changes noted.

It was previously believed that the amyloid kidney in patients with renal insufficiency and uremia was a small granular kidney—

FIG. 6.—Section of kidney of a patient who died of uremia 2 years after albumin appeared in the urine. Note the large number of tubular casts. The involvement of the glomeruli by amyloid was not more extensive in this case than in other cases where azotemia had not developed. It was felt that, in this instance, uremia resulted from tubular obstruction by casts.

the so-called amyloid contracted kidney. The early writers (Senator,[16] Bull[4]) claimed that the amyloid contracted kidney was not the result of pure amyloidosis, but represented a parenchymatous nephritis or an arteriosclerotic kidney, with amyloidosis superimposed. Fahr,[7a] however, found that chronic glomerulonephritis very rarely accompanied amyloid disease, and that arteriosclerosis played little, if any, part in the contraction of the kidneys that he had observed. He concluded that the contracted kidney was the result primarily of the amyloid deposition.

In recent years, cases of amyloidosis terminating in uremia have been noted in which the kidneys at autopsy were found to be large, pale and waxy. These reports show that the contracted kidney is comparatively rare and that the large pale kidney is the common finding. In none of the 7 cases of amyloidosis with renal insufficiency in Dixon's[6] series were the kidneys contracted. Rosenblatt[14] found 1 instance of contracted amyloid kidney in 8 patients that died of uremia. In our group, of 9 cases with renal insufficiency that were autopsied, in only 1 instance was a contracted kidney noted. The combined weights of the kidneys in the patients on whom necropsy had been performed are recorded in Table 3.

TABLE 3.—SUMMARY OF CASES OF RENAL AMYLOIDOSIS WITH RENAL INSUFFICIENCY.

Case.	Age.	Sex.	Etiologic disease.	Duration of etiol. disease (yrs.).	Duration of renal amyloid (yrs.).	Blood pressure.	Blood N.P.N., mg. %.	Blood creatinine, mg. %.	Edema.	Cause of death.	Heart wt. (gm.).	Combined wt. of kidneys (gm.).
1	30	M	Pulm. tb.	4	4 m.	114/70	45	..	0	Pulm. tb.		
2	27	M	Pulm. tb.	7½	1½	110/78	46	..	0	Pulm. tb.	190	Normal*
3	32	M	Pulm. tb.	2½	1½	100/85	48	..	+	Pulm. tb.		
4	60	M	Pulm. tb.	10	4 m.	100/70	48	..	+	Pulm. tb.		
5	48	M	Pulm. tb.	2	2 m.	108/64	60	..	+	Hemoptysis	280	Normal*
6	53	M	Pulm. tb.	5	4½ m.	135/90	69	..	+	Pulm. tb.		
7	16	M	Tb. hip joint	5½	2	100/68	80	..	+	Uremia(?)	200	320
8	36	M	Pulm. tb.	5	6 m.	...	84	..	+	Empyema	290	700
9	24	F	Pulm. tb.	10	1	...	90	3.7	+	Pulm. tb.		
10	56	M	Pulm. tb.	?	?	122/72	132	6.6	0	Uremia	400	452
11	16	M	Pott's dis.	7	?	...	138	..	+	Uremia		
12	29	M	Pulm. tb.	1½	?	90/60	150	..	+	Uremia		
13	58	M	Pulm. tb.	3½	1	146/98	156	8.6	+	Uremia		
14	44	F	Pulm. tb.	9	1½	82/60	168	6.6	+	Uremia		
15	63	M	Pulm. tb.	8½	2	135/98	180	5.5	0	Uremia		
16	35	M	Pulm. tb.	10	3½	115/80	192	..	0	Uremia	270	710
17	45	F	Pulm. tb.	4	1	116/80	228	6.0	0	Uremia		
18	25	F	Pulm. tb.	6	2	96/70	240	7.5	+	Uremia	200	610
19	32	M	Tb. hip joint	?	?	100/60	240	9.8	0	Uremia	350	525
20	42	F	Pulm. tb.	14	3½	190/98	250	10.8	+	Uremia	315	280

* The kidneys were not weighed, but appeared normal in size.

Microscopically, the earliest changes of renal amyloidosis are noted in the glomeruli and in the walls of the arterioles. Bell[2] and others have shown that the amyloid is deposited on the intima of the glomerular capillaries and in the muscularis of the arterioles. It is also occasionally present in the basement membrane of the tubules and in the interstitial tissue. With the progression of the disease there is an increasing deposition of amyloid in the glomeruli so that eventually the entire glomerulus appears as a ball of amyloid substance (Fig. 4); it is not surprising, in these instances, that uremia should develop. Fahr[7a] stated that even in advanced amyloidosis, the glomerular circulation may be good. However, if the process continues the capillary flow may eventually be completely obstructed. Finally the whole glomerulus may shrink and the amyloid be replaced by hyaline material (Fahr[7a]) (Fig. 5).

The associated changes of tubular atrophy and interstitial fibrosis are probably directly due to the impaired glomerular circulation. Fahr[7a] believes that tubular compression by interstitial amyloid or by tubular casts may account for a considerable part of the tubular atrophy in late stages, but Bell[2] believes this to be rare. Our studies agree with Bell on this point.

Tubular casts vary in number. In some instances, the casts are quite numerous and, in fact, may be sufficient to obstruct most of the tubules and thereby produce uremia (Fahr,[7a] Bell[2]). One of our cases (Fig. 6) developed uremia apparently on this basis since there was insufficient amyloid deposition in the glomeruli to account for the renal insufficiency.

As a general rule, with increasing duration of the amyloid disease, there is a progressive deposition of amyloid in the glomeruli. This is demonstrated in Figs. 1, 2, and 3, and tends to support the clinical observation that the longer the duration of renal amyloidosis, the greater is the probability that renal insufficiency will develop. However, there are some cases in which the amyloid is deposited very rapidly, and others in which the process is a slow one.

Conclusions. Between January 1, 1935, and August 1, 1937, there were 189 cases diagnosed as amyloidosis at Sea View Hospital; of these, 93 were classified as renal amyloidosis and are analyzed in this report.

Kidney insufficiency and uremia are prone to develop within 3 years of the onset of renal amyloidosis.

Hypertension is not common in the kidney insufficiency of renal amyloidosis; when it does occur it usually accompanies a contracted amyloid kidney.

Large waxy kidneys are the ordinary finding in the uremia of renal amyloidosis; contracted kidneys are the exception.

Renal insufficiency may be produced either by shutting off of the circulatory flow in the glomeruli or by plugging of the tubules by casts.

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DIABETES INSIPIDUS WITH BIG BLADDER (CAPACITY 2 LITERS).

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An amazing instance of diabetes insipidus which caused no nuisance to the patient is worth recording. The explanation was the big bladder shown by Roentgen ray (Fig. 1).

Case History. Mr. P. W. was born in Hungary, November 11, 1905, and at 22 he came to San José where he was working his way through school when first seen. His family history revealed no developmental anomalies. He had been under observation for occasional pain in the right flank. He had polyuria without pollakiuria, a most unusual phenomenon. With regard to possible brain infections or injuries, he remembered only being told that as a young child he fell over backwards in his chair. He has never been sick in bed for a week nor had any peculiar fevers.

Bladder. The polyuria was already existent in 1913 at the age of 8 years, when it amounted to about 8 liters per day; at its worst, at the age of 15, he estimated it as 10 or 12 liters. No incontinence. No discomfort such as might be expected from the big bladder. No pain on urination. Gonorrhea denied. Frequency of urination has been at most 4 times during the day and once during the night, and generally less.

On removing a gangrenous appendix in March, 1928, Dr. H. G. Jones and Dr. T. V. Moore, of San José, made the following observations: Fluid was found coming from a multilocular cystic tumor which filled the pelvis and extended high into the abdomen on the left side. The tumor was evacuated through a small opening, yielding about 5 liters of clear straw-colored fluid. The tumor lay in front of the parietal peritoneum, and was attached above to the umbilicus and below to the bladder. They believed it to be an unobliterated embryologic urachus and to consist of 3 or 4 sections communicating with each other and with the bladder. It was thought inadvisable to attempt removal of the cyst at the time.

On August 14, 1928, the patient was seen (E. R.) and promptly sent to Lane Hospital for Roentgen ray examination. Dr. R. R. Newell's extraordinary film is reproduced in Fig. 1 and his report follows: "*X*-ray of bladder, injected. The bladder is very large, and continues in a pouch of equal diameter and upward and slightly to the right, above the level of the crests of ilia. The outline is smooth but slightly wavy. The clinical diagnosis of cyst of the urachus would account for this very well." And a week later: "*X*-ray of bladder, injected, for comparison with previous films. Another injection in smaller quantity shows the bladder well rounded out, but the sac projecting upward and the right much less distended than at the first examination. We have demonstrated some difference in elasticity of the wall of the sac and of the bladder itself, but remarkably it seems to be the sac which is more tonic." The capacity of the distended bladder may be esti-

* The lamented death of Dr. Rixford on January 2, 1938, left the manuscript to be completed with the help of his records but without his criticism.

FIG. 1.—Two-liter bladder with diabetes insipidus.

FIG. 2.—Bladder with cord tumor, capacity 2900 cc

mated from the radiogram. Let us assume that the geometric shape approximates a prolate spheroid, that is, figure generated by an ellipse revolving about its major axis; call the longer semi-axis a and the shorter semi-axis b; then the volume wanted is $\frac{4}{3}\ ab^2$. On the film we measure the two diameters, multiply by $\frac{3}{4}$ to correct for magnification, and get 18.4 and 10, whence $a = 9.2$, $b = 5$. Hence the volume was 963 cc. at that time.

Operation (E. R.) was done on December 22, 1928, to determine whether there was an obstructing urethral bar or valve, or in case of finding a cyst of the urachus, then for its excision. Median incision; the bladder extended practically to the level of the navel, entirely within the peritoneum, hence not a urachal cyst. The abdomen was closed and bladder opened through a suprapubic incision, extraperitoneally; it was normal except for roughness and enormous thickening of the muscular wall such as found with an old hypertrophic prostate; the rugæ being in the upper extension of the bladder as well as the lower, and between these two parts no line of demarcation. A sound was introduced downward from the bladder into the urethra and met with obstruction, but when passed from below entered into the bladder without difficulty; this suggested a congenital valve in the prostatic urethra. Cystoscopy was done, January 16, 1929, by Dr. R. L. Rigdon, with negative findings, and the next day the patient was discharged. In May, 1929, the patient wrote with gratitude reporting himself "healthy and strong."

Diabetes Insipidus. Inasmuch as the large amount of urine passed caused the patient no trouble, the amount of attention given to the symptoms had been slight. Pituitrin, 0.5 cc., had been injected once a day for 10 days in November, 1930, the urine volume was not measured but appeared unchanged; the only effect noticed was flushing of the face developing within $\frac{1}{2}$ hour and lasting 3 hours after each injection.

The 24-hour amount of urine was first measured, June 9, 1929, as 5760 cc. During the 4 days here there were successively 8332, 6851, 6494, and 5636 cc., averaging 6828 cc. The single specimens in each 24-hour period were only 4 in number, their quantity varying from 905 to 1898 cc. Evidently the bladder capacity at this time was nearly 2 liters.

The NaCl output for the first 24 hours on an unrestricted diet was 12.8 gm., then on a measured diet of C. 195—P. 75—F. 85—Calories 1845 during the next 3 days fell to 5.9, 2.7, 1.7 gm. In short, some improvement.

The body weight fell from 70.3 kg. (155 lbs.) net on admission to 63.5 kg. (140 lbs.) net on discharge; a notable loss of tissue fluid.

Albumin was present in only the slightest possible trace by the heat and acetic test, while with Tsuchiya's reagent there were successively 600, 563, 468, and 396 mg. per 24 hours, as against normal of 50 to 100 mg.

Treatment. Several procedures were considered and discarded: 1, prolonged low-salt diet; 2, pituitrin subcutaneously (unsuccessful in the course stated above); 3, lumbar puncture, while said to cause dramatic decrease in output, was not done because the patient neither made complaints of his head nor showed changes in visual acuity or fields.

After-history. The patient was evidently alive on March 11, 1936, and on December 16, 1936, when physicians wrote asking for prior records; these were sent, with request for information on his condition; none was returned. Such are the difficulties of following up a remarkable condition.

Bigger Bladder. A cord bladder may be even more monstrous. For comparison we reproduce in Figure 2 an unpublished Roentgen ray of the case reported from a different angle by Towne and Reichert.[1] The Roentgen ray report by Dr. Edward Leef reads: "Filling the entire pelvis and lower abdomen up to the third lumbar vertebra, we see a large spherical area of increased density which represents a very large, completely filled urinary

bladder."* The size estimated by the same method as before, is defined by the corrected diameters 21.8 and 16.0 cm., whence the volume 2922 cc. Even greater capacity was anticipated on first comparing Figure 2 with Figure 1, but this is demonstrable as merely an optical error by noting the proportionately larger scale of the pelvis in Figure 2.

Summary. A case of diabetes insipidus which was free of discomfort owing to the storage capacity of a big bladder is reported, illustrated with a radiograph. Also, for comparison a radiograph of a less rare but even bigger bladder associated with cord tumor.

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A SYNDROME CONSISTING OF AFFECTIONS OF THE KIDNEY, STUNTED GROWTH, RICKETS AND DISTURBED CYSTINE METABOLISM.

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In 1924,[12] the above-mentioned conditions were found occurring together in 4 cases of young children.* One may ask whether it was justified to unite the clinical, anatomic and histologic symptoms into one syndrome. Was this combination perhaps characteristic of a definite infant disease or should it be considered as the fortuitous occurrence of different diseases in the same patient?

Until very recently it seemed that in this case one had happened to come across a very uncommon coincidence of pathologic changes. But in 1936 and in the beginning of 1937,[4 17] similar observations in infants were reported from London and from Göttingen, so that now 7 cases have been published. The latter authors were also struck by the coincidence of the above-mentioned pathologic conditions. It is worth while to ascertain once more, in the light of recent researches, the possible correlation between the symptoms.

Of the cases reported, 5 are boys, aged 21 months, 1½, 2, 3 and 16 years, and 2 girls, aged 14 months and 12 years.

These case reports now enable us to distinguish an infantile and a juvenile form.

Only twice was hydrocephalus internus diagnosed, which shows that this anomaly need not be present; perhaps the rickets accounts for it. Polydipsia, polyuria and also glycosuria have not been ascertained in all cases, and probably are dependent upon the renal affections. No histologic changes were found in the hypophysis in the cases in which this organ could be examined. During the whole

* In the beginning of this century E. Kaufmann made a similar observation with a boy of 21 months. Abderhalden[1] was able to ascertain cystinuria in 3 generations of this family.

illness, if it is accompanied by glycosuria, the blood sugar percentage is not increased. The German authors, in their case of a boy of 1½ years, speak of renal diabetes. The English authors, in the case of their first patient, think they can explain the glycosuria by a diminished glucose tolerance.

In all cases there are serious affections of the kidney, but they do not show the same anatomic and histologic changes. In some cases, they are distinct symptoms of a very serious albuminous degeneration (nephrosis), in other cases there exists an acute, non-purulent pyelonephritis or an interstitial proliferative nephritis; in 1 case the latter disease affected the incompletely developed kidneys (boy of 1½ years).

The stunted growth and development in early youth are very conspicuous. The 12-year-old girl is a dwarf, but this cannot be said of the 16-year-old boy. Fully developed rickets is always present, except in the case of the boy of 16, yet until his seventh year he was under treatment for this disease. Shortly before his death rachitic symptoms were not (particularly) observed, neither was the skeleton specially examined after death. In the only case where the parathyroid glands were examined (the 12-year-old girl), they appeared to be enlarged.

A surprise for pathologist and clinician is the postmortem discovery of characteristic crystalline cystine deposits in the different organs, most obvious in the spleen. In none of the cases was examination for cystinuria made, though from an observation in a 14-month-old girl it should be accepted that it can exist. At the postmortem examination of this girl cystine calculi appeared to be present in renal pelvis and ureter. In this case, however, the cystine deposits in the organs were not visible macroscopically, but only after an extensive microscopic search.

In this connection, attention should be especially given to English and American researches attempting to show the correlation between affections of the kidney and rachitic (or similar) symptoms, and between affections of the kidney and dwarfism. The term "renal rickets" and "renal dwarfism" have become established, implying that in these cases the affection of the kidney causes the rickets and the dwarfism. Fletcher,[7] Miller and Parsons,[13] Barber,[3a] Shipley *et al.*[18]

If we inquire which affections of the kidney are found in connection with rickets and dwarfism, we see that repeatedly interstitial proliferation of the connective tissue, sometimes accompanied by slight inflammatory changes of the glomeruli, is found. In a number of cases bilateral, congenital cystic kidneys are found, in 1 case combined with an excessive proliferation of the connective tissue. In only a few cases pyelonephritis has led to a progressive renal insufficiency, combined with the above-mentioned anomalies of the skeleton. There have also been described: a bilateral hydro-ureter

and hydronephrosis with atrophy of the kidneys; renal calculi with destruction of the renal tissue and proliferation of the connective tissue; absence of one kidney, the other showing cystic degeneration; deformity of the kidneys and finally a moderate glomerular sclerosis of the kidney with extreme lipoid nephrosis combined with arteriosclerotic changes of the aorta and the small vessels.*

As to the etiology of the most frequent renal affection, namely, chronic, interstitial, proliferative nephritis, one is still completely in the dark. Worth mentioning is Welz's opinion, based upon the literature and upon two observations of his own, that incomplete development of the kidneys is primary, and that proliferation of the connective tissue is brought about secondarily by different factors.

By prolonged observation of similar cases Barber[3b] and other authors could prove that in youth the affections of the kidney were evident many years before the changes of the skeleton, and sometimes even could be diagnosed from birth. It was natural to surmise a causal relation between these affections of the kidney and the pathologic changes of the growth of the skeleton that appeared later on. However, we should be circumspect, for injurious influences, not yet known it is true, sometimes in combination with congenital inferiority of the organs, may bring about changes of both organs in different periods.

Only in 40% of these cases is chronic, infantile, interstitial proliferative nephritis, leading to a renal insufficiency, accompanied by the above-mentioned maladies of the bones.[9]

On the other hand, the results of von Balogh[2] should be considered: having so injured the kidneys of young rats, that functional disorders resulted, he saw a considerable retardation of growth after from 5 to 8 weeks, as compared with healthy rats from the same litter.

"Renal" dwarfism as such is characterized by the fact that normal proportions of the parts of the skeleton remain unchanged. It may be difficult to distinguish from infantile dwarfism, when in a case of renal dwarfism there is also defective development of the secondary sex characteristics.

Rickets leads to deformities of the bones, possibly resulting in a dwarfish *build*. In this case, the cause of the dwarfism lies in the distortions of the vertebral column and of the lower extremities; yet *sensu stricto* this dwarfish build should not be regarded as rachitic dwarfish *growth*, which is the result of the delayed or defective longitudinal growth, as a consequence of serious impairment of the epiphyseal cartilages of the lower extremities, especially of the femora.

According to the descriptions, "renal rachitis" is rather changeable and variable in its pathologic aspect, though Hamperl and Wallis[9] in 1 of their cases do not hesitate to admit that clinically

* An excellent review of the subject is given by Alfred Welz.[20]

and pathologico-anatomically the changes of bone could not be distinguished from the changes caused by genuine rickets.

In cases of genuine rickets there is, as a rule, hypophosphatemia, the calcium percentage is normal or a little too low; in "renal rickets" it is just the reverse, for we find hyperphosphatemia and hypocalcemia. Antirachitic treatment with ultraviolet rays, cod-liver oil and vigantol with few exceptions does not give any improvement in "renal rachitis;" on the contrary, we see the disease grow worse.

Welz,[20] from his critical study of the literature and from his own observations, suggests that renal dwarfism should be subdivided into two forms: one with normal proportions and no deformities of the bones, and one with deformities.

Now what is the causal relation between the insufficient sclerotic kidney and dwarfism and the rachitic changes? On this subject no less than 7 hypotheses have been published. It would take too long to review them all. The theory of Hamperl and Wallis[9] may be specially mentioned in connection with the present subject: the disturbance of the metabolism in consequence of renal insufficiency would by itself be unable to bring about the rachitic changes in the skeleton and the dwarfism, the existence of a particular disposition in the patient has to be surmised as well. These authors admit also the possibility of the same injurious agent causing the changes in both kidney and skeleton.

In the light of these recent researches it is tempting to put the renal affection in the center of the pathologic picture and to regard stunted growth and rickets as dependent upon these. Russell and Barrie[17] do not hesitate to speak of one of their cases as "renal rickets;" Beumer and Wepler[4] speak likewise of "renal" dwarfism, and in their case (a boy of 1½ years) the development of the kidneys also was retarded and an interstitial, proliferative inflammation had developed.

These authors also emphasize the resemblance of this affection and of the so-called "glycosuric dwarfism with hypophosphatemic rachitis" (Fanconi[6]).

The 3 Leyden cases, however, do not correspond to this view, as the renal changes were acute; the acute cellular pyelonephritis became manifest in a 2-year-old boy, who showed from birth defective physical development and also suffered from fully developed rickets; in the other cases, the albuminous degeneration of the kidneys did not appear to have existed for a long time, whereas the skeleton already showed symptoms of florid rickets, and the stunted growth and development of the 3-year-old boy had existed for 2 years. For the time being it will be wise to wait for more, particularly clinical data, before coming to definite conclusions. The combination of renal affections, stunted growth and rickets need not by any means be "accidental;" but it may be that in these cases both

kidneys and skeleton of the patients are inferior, and consequently when exposed to injurious influences produce the pathologic changes mentioned. In this case, functional disorders of the kidneys may intensify the detrimental influence upon the skeleton.

What causes the deposition of cystine in the different organs? This uncommon symptom is mentioned in the literature only 7 times, always in combination with the other pathologic symptoms already discussed.

The following possibilities should be considered: Cystinuria*[8] as a symptom of "cystine diathesis" was generally regarded as being the result of incomplete destruction of the cystine; according to Brand *et al.*[5] (cited after Beumer and Wepler[4]) the symptoms of "cystine diathesis" would be dependent upon the destruction of the cystine. Whether or not these children suffered from cystinuria, was never ascertained clinically. In 1 case, cystinuria very probably existed, judging from cystine calculi in renal pelvis and ureter (14-month-old girl). In Kaufmann's[10] case, Abderhalden[1] diagnosed cystinuria in 3 generations of this family. In the other cases, the members of the family were either not examined or the examination was negative.

Cystine, as a sulphur-containing amino-acid, takes a special place in protein metabolism. It cannot be formed by the mammalian organism, consequently it must be present in the food; the growth of young animals is stunted, if cystine is absent from their food. Mörner[14] claims to have proved that either all the sulphur in the protein, or the greater part of it, is bound to a group, which by hydrolysis produces cystine. Cystine is found in keratin, liver protein, products of pancreatic digestion *in vitro* and fibrin. However, according to more recent researches, there is yet another sulphur-containing amino-acid, called methionin (Müller,[15] 1923, cited after Beumer and Wepler[4]), that is found in casein and other substances. In growth experiments, it can completely replace cystine, without damage to the young animal. Conversely, however, cystine cannot replace methionin (Rose *et al.*[16]). Cystine is a normal metabolic product, that in very small quantities is excreted in the urine.

Cystine, administered[11,12] enterally or parenterally to young mice in large doses, impairs the renal parenchyma and causes granular (cloudy) swelling of the convoluted tubules and even necrosis of the tubuli recti of the medulla.

The possible causes of the cystine deposits in these infants are many. Considered in connection with the stunted growth, the deposits might be due to the infants not being able to assimilate the cystine; the unassimilated cystine, incompletely excreted on account of the impaired function of the kidney then crystallizing in the organs. Just as, according to some authors, polydipsia,

* Cystinuria in consequence of a serious vital autolysis of the liver, as is found sometimes in cases of acute or subacute yellow atrophy is left out here.

polyuria and glycosuria may be of renal origin, so the affected kidneys in these cases would be able only incompletely to excrete the cystine, causing thereby retention of cystine. Finally, this retention can be brought about, as in cases of cystine diathesis, by an incomplete destruction of cystine in combination with an incomplete excretion by the diseased kidneys.

Russell and Barrie[17] mention the case of a 13-year-old boy, who since his early youth suffered from cystinuria and cystine calculi and later developed chronic nephritis; however, after his death no cystine deposits in the organs could be demonstrated.

Thannhauser[19] is of the opinion that in "cystine diathesis" there is no absolute impairment of cystine destruction. The cystine administered with the food can still be partly used, so that this diathesis ought not necessarily to lead to general and serious impairment of growth and of nutrition.

Finally, should be mentioned the possible causal rôle played by cystine in the development of infantile renal affections, as suggested by the above mentioned experiments with young mice.

Summary. A syndrome consisting of *affections of the kidney, stunted growth, rickets* and *disturbed cystine metabolism* is described as characteristic of a definite disease, met in 7 children, of whom 5 are boys, aged 21 months, 1½, 2, 3 and 16 years and 2 girls, aged 14 months and 12 years.

One can distinguish an infantile and a juvenile form. Renal rickets (renal dwarfism), discussed in relation to the above-mentioned syndrome, is regarded as different from it.

The disturbance of the cystine metabolism is thus far detected only at the postmortem examination. The possible causal part played by cystine in the development of infantile renal affections, as suggested by Lewis and Lignac's experiments with young mice, is mentioned.

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A STUDY OF SILICOSIS.*

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The present study was instituted because of the increasing importance assumed by the disabilities resulting from silicosis, and, in order to ascertain the extent to which this disease is present among ex-service men under treatment in the Veterans' Administration.

A review of the clinical data of the cases indicates the inadequacy of the occupational histories in the cases of patients suspected of having silicosis, as secured and recorded in routine hospital practice. The usual procedure is to record the occupations the patient was engaged in prior to his hospitalization without describing in detail the daily hours of work, the concentration of dust, the total time of exposure to dust, and the total period of time engaged in siliceous work. Such data are essential in establishing a diagnosis of silicosis.

In recent years, silicosis has assumed importance as a disease entity. The reason for this is the rapid industrial growth during the past quarter of a century with a resulting increase of siliceous hazards. Sayers and Jones[5] are of the opinion that nearly 1,200,000 persons are engaged in dusty occupations in which there is a silicotic hazard. This figure applies only to the manufacturing and mechanical industries. Metal mining, quarrying, stone cutting and foundry industries are also sources of exposure. Sandblasting, grinding, polishing, and hardrock drilling in coal mines, contribute materially to the incidence of the disease.

It may be said that silicosis now constitutes the greatest single occupational hazard in the country. The seriousness of silicosis is due to the fact that tuberculosis is a very frequent complication, thus causing the silicotic to be a menace to fellow workers and to his family. It is estimated that pulmonary tuberculosis is the cause of death in 75% of silicotics.

Present Study. The present study includes a detailed analysis of the clinical, and statistical data of a group of 167 silicotic veterans, 120 of whom were alive at the time of the study and 47 were dead. Of the 47 deceased silicotics 23 had had postmortem examinations, the principal pathologic findings of which have been published elsewhere.

The largest number of the living patients were in the age group 40 to 49 years; the minimum age of the group was 37 years, the maximum age was 65 years; and the average age at the time of the study was 46 years.

* The study was planned and conducted with the coöperation of Drs. Leroy U. Gardner and H. L. Sampson of Saranac Lake, New York, and Dr. H. B. Williams of Veterans' Administration, Sunmount, New York. Assisting in the study were a number of medical officers of the Veterans' Administration. To all of these physicians the author is grateful for their splendid coöperation.

Age at Time of Inception. The age grouping of the silicotic veterans at the time of the inception of the disease shows that 50% of the total number gave a history of having acquired the disease within the age groups 30 to 39 years; and 32% within the age groups 40 to 49 years. The minimum age at the time of inception of the disease was 23 years, the maximum age was 67 years, and the average age was 39 years. Of the total number 60% acquired silicosis before the age of 40, and 40% after that age.

It would appear therefore that age *per se* is not an influencing factor, and that other factors play a more important rôle in the development of the disease. It must be realized that chronic respiratory and sinus infections are very apt to be present in the early as well as in the late periods of life, and it is disabilities such as these which predispose individuals to the development of silicosis. The onset of the disease during or after middle life is of frequent occurrence and its presence must be thought of in those engaged in siliceous occupations.

An effort was made to ascertain whether or not the type of siliceous occupation had any influence upon the age of inception of the silicotic disease. It was found that in the metal mining industry the average age at the time of onset was 39 years; in the coal mining industry the average age was 37 years; in the quarrying occupations the average age was 38 years; and among those engaged in miscellaneous siliceous occupations who incurred the disease, the average age at the time of inception was 43 years.

Correlation of Occupation With Type of Silicosis. Because of the prevailing opinion that the type of silicosis is dependent to a considerable extent upon the kind of silica dust inhaled, an effort was made to correlate these data to see whether or not it would be possible to confirm such a relationship, The findings indicate that there is no apparent tendency for any of the siliceous occupations to produce a particular type of silicotic disease.

Length of Exposure. A comparison of the periods of exposure of the living and dead silicotics indicates that, as a general rule, the exposure time in the dead silicotics was shorter than in the living cases. One may infer that the deceased silicotics were more prone to the development of silicosis than were the living cases. These findings may lend strength to the opinion held by some that there is an individual susceptibility to the disease.

It was further found that silicosis may develop after as short an exposure time as 1 year; the usual minimum time is from 3 to 5 years for the various siliceous occupations. The average exposure time in the case of the living silicotics was 13.2 years and among the deceased silicotics 12.6 years.

The conclusion is reached that in silicosis the development of the disease is dependent upon a number of factors, such as the susceptibility of the individual to silica dust, the type of dust, its concentra-

tion, as well as the length of exposure. It is believed that individual susceptibility to silica dust should be stressed more than has been done in the past, inasmuch as the data in this study point to the probability of the existence of such a factor. The individual susceptibility may be due to a number of conditions such as a preëxisting respiratory or sinus disease, pathologic-anatomic development of the nasal passages, and the possibility of an increased sensitivity to silica dust.

Duration of Disease. The clinical course of silicosis, as well as the duration of the disease, differs in various occupations and industries. The data showing the duration of life from the onset of the disease to the date of this study in the living cases, and to the date of death in the deceased cases, revealed some very interesting information. It was found that the average duration of the disease in the living cases was 9 years. It must be understood that the figures are not final, inasmuch as they represent the duration of the disease in living silicotics up to the time of this study. The average duration of the disease in the case of 30 deceased silicotics was found to be 6 years. A comparison of the data in the living and deceased silicotics shows that the duration of the disease among the deceased silicotics was shorter than among the living cases.

There are certain factors which have an influence upon the duration of the disease in silicotics. Some of these are extrinsic, such as the type of silica dust, its concentration, and the length of exposure —these determine the extent of the silicotic lesions. The other factors are intrinsic and are dependent upon the progressiveness of the silicotic disease, which is influenced by the rate of nodule formation; the presence of a preëxisting or supervening tuberculous or non-tuberculous infection; and the immunologic response of the silicotic host to the infection.

Were it not for the intercurrent infections, the duration of life in silicotics would not be materially affected. However, when infection complicates the disease, the resistance of the individual may become greatly reduced and result in a shortening of the life span. It may therefore be concluded that the duration of life in silicosis is dependent to a large extent upon the immunologic response of the silicotic to the complicating infection present in a particular case.

Life Expectancy and Survival Period in Silicosis. The data on the life span of persons who enter the different siliceous occupations showed that among 73 living cases the total survival period, which includes the period from the date of entry into the occupation to the date of the study, was from a minimum of 6 years to a maximum of 43 years; the average time was 22.1 years. In a group of 30 deceased silicotics, the shortest duration of life, that is, the shortest period from the date of entry into the occupation to the date of

death, was 8 years, the maximum duration of life was 51 years, and the average duration of life was 19.1 years.

Classification of Silicotic Disease Used in Study. For the purpose of this study, the following Roentgen ray classification (Dr. H. L. Sampson) was used:

(*a*) First degree silicosis: The nodulations are 2 mm. or less in diameter.

(*b*) Second degree silicosis: The nodulations are from 2 to 4 mm. in diameter.

(*c*) Third degree silicosis: The nodulations are 4 mm. or more in diameter.

(*d*) Conglomerate silicosis: A coalescence of the nodulations, in which the Roentgen ray shows conglomerate shadows, usually with associated emphysema. Conglomeration is due to previous trauma of the lung parenchyma, the result of bacterial invasion or lymph flow disturbance.

(*e*) Silicosis with infection: Characterized by silicotic nodulations in the form of Roentgen ray densities with fuzzy borders, and irregular in distribution; or shadows of mottling; these have ill-defined borders, vary in size, and lack uniformity in density and distribution.

(*f*) Silicosis with tuberculosis: Roentgen ray densities consist of fibrotic nodulations, fluffy and hazy in outline, with a superimposed tuberculous infection, characterized by pleuritic densities, Roentgen ray irregularities of the diaphragm, or cavity formation. The silicosis and the tuberculous infection exist more or less as separate entities.

(*g*) Silico-tuberculosis: This is a condition in which the Roentgen ray shows conglomerate fibrotic nodulations, pleural densities, irregularities of the diaphragm domes, or cavity formation. The lung changes are so extensive and the tuberculous and silicotic conditions are so closely interwoven that one is unable to show a separate background for either condition.

(*h*) Asbestosis: In the early stages the Roentgen ray findings may be described as showing a ground glass appearance in the lower parts of the lung fields. In the later stages, the haze spreads to the upper portions of the lungs with the appearance of very fine stippling that obliterates most of the normal markings. The pleural shadow is definitely thickened. A characteristic finding at times is the heart shadow which is enlarged, and, radiating from it into the lung fields is a series of heavy fibrous bands; the cardiac Roentgen ray appearance has been referred to as a "porcupine heart." Manifestations of tuberculosis and other infections in asbestosis are characterized by dense homogeneous shadows with mottling and cavity formation.

Classification of Cases. The classification of the silicotics included in this study showed that 30% were cases of silicosis of the first, second, or third degree; 11% were silicosis with infection; 42% were

silicosis with tuberculosis; 16% were cases of silico-tuberculosis; there was but 1 case of asbestosis included in the study.

Symptoms and Physical Signs. It is the general experience of clinicians that silicosis, especially in the early stages is difficult of diagnosis. Symptoms and physical signs may or may not be present, and, even if present it is necessary to support the clinical evidence with Roentgen ray findings. Even the Roentgen ray evidence is frequently obscured when emphysema is present. Accordingly, a study was made to ascertain the most frequent clinical symptoms and physical signs observed in the silicoses. It was found that these varied according to the type of silicotic disease and the character of the coëxisting complications.

In uncomplicated silicosis the most frequent clinical symptoms and physical signs noted were dyspnea, cough, chest pain, impairment of breath sounds, fatigue, râles, and loss of weight, in the order named.

The predominating clinical symptoms and physical signs noted when a non-tuberculous infection complicated silicosis were dependent upon the degree of silicosis, and the nature of the infection. Dyspnea was the most frequent symptom found; the next most frequent symptom was cough; this was followed by impairment of breath sounds, chest pain, fatigue, râles, and excessive expectoration of sputum, in the order named.

In silicosis complicated by tuberculosis the most frequent symptoms and physical signs were cough, dyspnea, chest pain, fatigue, impairment of breath sounds, loss of weight, râles, excessive expectoration of sputum, loss of appetite, and blood tinged sputum, in the order named.

Inasmuch as silico-tuberculosis is characterized by more extensive lesions than is usually seen in silicosis with tuberculosis, the clinical symptoms and physical signs are more accentuated than in the latter disease. The most frequent symptoms and physical signs of the group of cases of silico-tuberculosis were impairment of breath sounds, râles, dyspnea, cough, fatigue, loss of weight, chest pain, excessive expectoration of sputum, blood tinged sputum, and loss of appetite, in the order named.

Roentgen Ray Diagnosis of Silicosis and Its Complications. In a study of the Roentgen ray findings in uncomplicated silicosis, it was noted that the most frequent Roentgen ray evidence was accentuation of the linear markings; the next most frequent finding was beading along the course of the linear markings and at the bifurcation of the trunks; discrete nodule formation was next in frequency; and next came widening of the mediastinum. Emphysema was present in 42% of the group of 50 cases.

In silicosis with infection, the most common Roentgen ray findings in the order of frequency were mottling, widening of the mediastinum, diffuse haze or shadow extending inward from the

lateral pleura of the mid-portion of the lungs, prominence of the linear markings, beading along the course of the linear markings and at the bifurcations of the trunks, emphysema, discrete nodule formation, confluent nodule formation, and a combination of discrete and confluent nodule formation.

In silicosis with tuberculosis, the most frequent Roentgen ray findings were fuzziness and haziness of the outline of the silicotic nodules, fibrosis, caseation, mottling, and emphysema.

In silico-tuberculosis the most frequent Roentgen ray findings were fuzziness and haziness of the outline of the silicotic nodules, fibrosis, mottling, caseation, emphysema, pleurisy, and cavitation. It was noted that there was a greater incidence of pleuritic involvement in silico-tuberculosis than in silicosis with tuberculosis.

Complicating and Coëxisting Diseases. The clinical course and prognosis of silicosis are dependent to a considerable extent upon the coëxisting or complicating diseases. Silicosis *per se*, especially in the early stages, is not accompanied by very much disability. It is only when a complication supervenes that the silicotic gives evidence of disablement and an occupational handicap, and the prognosis may then become unfavorable.

Abnormal anatomic development of the nasal passages, respiratory infection, heart disease, sinus infection, or any condition which facilitates the inhalation of dust, or, which retards lymph flow, may act as a predisposing factor in the inception of silicosis. A person engaged in a siliceous occupation, who has arrested or quiescent tuberculosis, may develop silicosis earlier than usual, and after the onset of the disease, a reactivation of the dormant tuberculous disease may follow.

Heart disease complicating silicosis may cause extensive lung fibrosis which in turn may result in a strain on the heart, and may lead to an unfavorable course of the silicotic disease.

Accordingly, a coëxisting or complicating disease may affect adversely the clinical course as well as the prognosis of silicosis. Such a disease may have preceded the inception of silicosis and aided in its onset, or, it may have appeared as a supervening or complicating condition and caused a shortening of the life of the silicotic.

In the group of cases studied, it was found that the most frequent complications and coëxisting diseases were: 1, Pulmonary tuberculosis; 2, cardiovascular disease; 3, emphysema; 4, pulmonary infections; 5, bronchiectasis; 6, chronic pleurisy; 7, chronic bronchitis; and 8, dental diseases.

Pulmonary Tuberculosis. It is the consensus of medical opinion, based upon experimental evidence as well as clinical observation, that silicosis increases susceptibility to tuberculosis, which may hasten the silicotic process to a fatal outcome. It is the commonest and most important complication and is responsible for most of the

deaths among silicotics. Frequently it precedes the inception of silicosis and tends to hasten its onset.

Usually the complicating tuberculous infection arises in the advanced stages of the silicotic disease, although it frequently occurs in the early stages. When pulmonary tuberculosis appears, it is accompanied by the usual symptoms and signs characteristic of the disease.

Pulmonary tuberculosis may complicate silicosis in one of three clinical forms: As silicosis with tuberculosis; silico-tuberculosis; and as an acute bronchopneumonic type of the disease.

In the consideration of the total group of 167 cases, it was found that 97 gave evidence of pulmonary tuberculosis and 70 cases were without signs of tuberculosis, either clinically or roentgenologically. Of the 97 cases, 62 were alive and 35 had died.

Of the group of silicotics with complicating tuberculosis, the minimum length of time after exposure to silica dust before the patient gave evidence of tuberculosis was 2 years, the maximum time was 40 years, and the average length of time was 15 years.

In a study of a small group of cases in order to ascertain the period of time between the first clinical evidence of silicosis and the first signs of tuberculosis, it was found that the minimum time was 2 years; the maximum time was 10 years; and the average time was 6 years.

A study of the classification of 97 cases of silicosis complicated by pulmonary tuberculosis showed that 11% were incipient, 32% moderately advanced, 57% were far advanced tuberculosis. Tuberculosis complicated the early as well as the advanced stages of the silicotic disease.

Of the 97 cases 78 gave evidence of tuberculous disease in both lungs; in 14 the right lung was involved; and in 5 the left lung gave evidence of tuberculosis.

In a detailed study of the most common sites of the tuberculous disease it was found that of the 97 cases, in 38% all lobes of both lungs were affected; in 11% the right upper lobe was affected; in 7% the right and left upper lobes, as well as the right middle lobe; in 5% the left upper lobe; and among the rest of the cases the site of the pulmonary disease varied.

In a study of the pathologic changes found in the 97 patients with complicating tuberculosis, it was found that the largest number gave evidence of caseation and fibrosis; the next largest number showed the presence of caseation, fibrosis and pleurisy; the rest of the patients gave evidence of various combinations of pathologic changes, ordinarily seen in tuberculous disease of the lungs.

Cardiovascular Diseases. The heart may show evidence of disease in silicosis. The cardiac changes may consist, in some instances, of a slow progressive dilatation and hypertrophy, the result of an obstruction to the pulmonary circulation due to extensive fibrosis of

the lungs. The cardiac failure is insidious and brings about a train of symptoms and pathologic conditions such as chronic passive congestion of various organs, ascites, hydrothorax, dyspnea, and so on.

Of 120 living silicotics under observation, 50 (41.7%) gave evidence of cardiovascular disease. Of this number, 28 patients showed the presence of cardiac hypertrophy, dilatation, or a combination of the two conditions; 16 showed the presence of fibrosis of the myocardium; and 21 gave evidence of arteriosclerosis.

Of 24 deceased cases, who had not been autopsied, 13 showed the presence of cardiovascular disease, and of the number 6 were cases of cardiac dilatation or a combination of hypertrophy and cardiac dilatation.

In a series of 23 autopsied cases studied by the writer and reported elsewhere, it was found that the cardiovascular system was a frequent site of the disease. Hypertrophy or dilatation of the heart, or a combination of the two conditions, was found in 18 of the 23 autopsied cases. The age incidence in the group of 18 cases was from 27 to 72 years; the average age was 47.4 years. It was found that in the 18 cases, cardiac hypertrophy, cardiac dilatation, or a combination of the two conditions, was present in the early as well as in the advanced stages of silicosis.

Emphysema. Considerable difficulty is frequently experienced in recognizing emphysema. It has been shown that the most reliable means for diagnosing this condition is by lateral chest roentgenograms. There is an increase in the space between the anterior cardiac border and the anterior chest wall, due to hyperaëration of the left and right upper lobes of the lung. In addition, there is a considerable increase posteriorly of the cardiospinal space, which is represented by lung tissue of the right and left lower lobes. These two areas give evidence of increased radiability. While depressed diaphragmatic domes are common in emphysema, they are not a reliable diagnostic sign.

Emphysema is ordinarily more prevalent in the advanced stages of silicosis. However, in a study of clinical as well as autopsy material, it was found that emphysema was also quite common in the early stages of the silicotic disease. Among the group of 167 cases, 99 (59%) gave evidence of emphysema.

Pulmonary Infections. Proske and Sayers[1] hold that in general the silicotic lung is the site of bacterial infection due probably to irritation of the respiratory tissues by the inhaled dust particles; this weakens the mucous membrane and renders it susceptible to bacterial action. The toxic influence of certain dusts on the tissue may be a contributing factor. These observers state that while tuberculosis is the principal complicating disease in silicosis, other infections, such as pneumonia, lung abscess, and bronchiectasis, are frequently encountered.

In a study of the group of 167 silicotics, it was found that 56 (34%) gave evidence of pulmonary infection; this number consisted of 39 cases of chronic bronchitis, 11 cases of bronchiectasis, and 6 cases of chronic pharyngitis.

Bronchiectasis. According to Proske and Sayers,[1] bronchiectasis may be due to infection or inflammation of the bronchi. Although the latter in itself would not be sufficient to cause a widening of the bronchi, there may be an added mechanical factor in the distention due to the loss of elasticity of the bronchial wall, and the presence of pleural adhesions which draw on the bronchi from all sides and cause them to distend.

The question arises as to the manner in which the bronchi become the site of infection. It is believed that oral and dental diseases, such as gingivitis and pyorrhea, are etiologic factors. According to Proske and Sayers, silicotic individuals inhale large quantities of dust during working hours, which may become contaminated with the infectious material from the teeth and gums. The contaminated dust particles which pass beyond the ciliated epithelium of the respiratory tract, reach the alveoli, where they cause irritation, and stimulate the proliferation of the microörganisms which are usually present with the dust particles. Of the group of 167 silicotics, 11 (7%) gave evidence of bronchiectasis.

Chronic Pleurisy. Chronic pleurisy is ordinarily not found in silicosis, but appears in cases of silicosis complicated by pulmonary infection. There are localized areas of thickened pleura which are commonly seen over superficial nodulations in silicosis. These are fibrotic nodulations rather than inflammatory areas. Russell, *et al.*[3] found a high incidence rate of pleurisy in silicosis, particularly in those engaged in granite and hard coal occupations. In a study of the clinical and postmortem material of silicosis in veterans, the writer found pleural involvement present in 66 (40%) of the cases.

Prophylaxis and Treatment. The treatment of silicosis is principally prophylactic. It should consist of the introduction of engineering methods to control the dust at its point of generation, and to remove the dust from the atmosphere. Studies of the working environment to ascertain the dust concentration, size of dust particles, and so on, should be made periodically with a view to reducing dust hazards to a minimum.

It is important that cases of silicosis be detected and diagnosed in the early stages of the disease, so that the subjects may take steps to avert pulmonary infection, particularly tuberculosis. It is the complicating infection which is a serious problem in silicosis, inasmuch as it changes an ordinarily favorable clinical course of silicosis to an unfavorable one, with poor prognosis. The silicotic has a comparatively normal capacity for work until the inception of the complicating infection, after which disablement and an occupational handicap follow.

For the purpose of detecting the earliest evidence of silicotic disease, persons who work at siliceous occupations should undergo periodic physical examinations, including roentgenography of the chest—this should preferably be done semi-annually.

Then too it might be advisable to apply the tuberculin test routinely at these periodic examinations so as to detect tuberculosis infection as early as possible.

The question is frequently asked whether or not the silicotic subject should be removed from his siliceous occupation when the disease is diagnosed. According to a number of observers, the silicotic disease progresses to an advanced stage, even though the subject is removed from the siliceous environment. However, Sappington found that after removal of silicotics from the siliceous exposure, 20% in the first stage of the disease progressed; 40% in the second stage; and all of the silicotics in the third stage of the disease gave evidence of progressive silicosis. Accordingly, it would seem that in order to hold the disease in abeyance, prolong the life of the silicotic, and extend his occupational usefulness, it is essential that the disease be diagnosed in the early stages and, if practicable, the subjects be reassigned to less dusty work. It is particularly important that silicotics with complicating tuberculosis be removed from their dusty environment so that employees working in close proximity may be protected from infection.

Another problem which deserves consideration is the hospital treatment of silicotics. Patients with uncomplicated silicosis should not be treated in tuberculosis sanatoria because of the danger of exogenous infection; they should preferably be treated in general hospitals.

Mortality Among Silicotics. In a study of anthraco-silicosis in Pennsylvania, made by the U. S. Public Health Service,[4] it was found that the mortality from respiratory diseases was much greater among the miners than in the general adult population of the country. Russell[2] states that the influence of dust on the mortality from tuberculosis is clearly demonstrated in the statistics of the granite industry. The data show that as a result of the excessive dust created by the use of pneumonic tools, the tuberculosis death rate had increased rapidly, from 1.5 per 1000 in the 1890–1894 period to 19.5 per 1000 in the 1924–1926 period. In a study of the mortality statistics among Barre, Vermont, granite workers, Russell found that there had been an excessive death rate from pneumonia and other respiratory diseases. It is a well known fact that while in recent years the death rate from pulmonary tuberculosis in the general population has been reduced, there has been an increase of the tuberculosis death rate during the same period among workers in dusty trades.

Of the group of 167 silicotics, 47 were reported to have died, 30 of the 47 cases died within the age period, 40 to 49 years. The mini-

mum age at the time of death was 27 years; the maximum age was 72 years; and the average age was 45.6 years.

In a study of the duration of the silicotic disease in the group of silicotics who had died, it was found that the minimum duration was 6 months; the maximum duration was 16 years; and the average duration was 6 years.

Summary and Conclusions. 1. Silicosis is the chief occupational disease in this country. The seriousness of silicosis is due to the fact that it is conducive to the inception of pulmonary tuberculosis. Tuberculous silicotics are a source of danger to their fellow workers as well as to members of their families, because of the ease with which tuberculous infection is transmitted. The disease results in a great economic loss to society.

2. A study of the classification of silicotic disease in a group of 167 veterans showed that 30% were classified as first, second, or third degree silicosis; 11% were cases of silicosis with non-tuberculous infection; 42% were cases of silicosis with tuberculosis; 16% were classified as silico-tuberculosis; and 1 case was diagnosed as asbestosis.

3. The various siliceous occupations act differently in causing silicosis. The differences are due to a number of factors such as the silica content of the dust, the size of the silica particles, variation in the time of exposure, the presence of organic or non-siliceous dusts mixed with silica, and the probability of the existence of an individual susceptibility.

4. In the group of cases studied, it was found that the most frequent complications and coëxisting diseases were pulmonary tuberculosis, cardiovascular disease, emphysema, pulmonary infections, bronchiectasis, chronic pleurisy and dental diseases.

5. In a study of the classification of the 97 cases of silicosis complicated by tuberculosis, it was found that in 11% the tuberculous disease was classified as incipient; in 32% it was moderately advanced; and in 57% far advanced.

6. The cardiovascular system may show evidence of disease silicosis. The abnormal cardiac changes are characterized by a progressive dilatation and hypertrophy due to obstruction of the pulmonary circulation, the result of extensive fibrosis of the lungs. Of 120 living silicotics, 50 (41.7%) gave evidence of disease of the heart or blood vessels; of this number 28 showed the presence of cardiac hypertrophy, dilatation, or a combination of the two cardiac conditions; 16 showed the presence of fibrosis of the myocardium; and 21 gave evidence of arteriosclerosis. Of 24 deceased silicotics on whom no postmortem examination was done, 13 showed the presence of cardiovascular disease, of which number 6 were cases of cardiac dilatation, or, a combination of hypertrophy and cardiac dilatation. In a series of 23 autopsies on silicotic subjects and reported elsewhere by the writer, hypertrophy or dilatation of the

heart or a combination of the two conditions was found in 18 instances. These cardiac conditions were found in the early as well as in the advanced stages of silicosis, also in silico-tuberculosis.

7. While tuberculosis is the principal complicating infection in silicosis, other infections, such as pneumonia, lung abscess, and bronchiectasis, are frequently encountered. Upper and lower pulmonary tract infections were found in 56 (34%) of the group of 167 silicotics; there were 39 cases of chronic bronchitis, 11 cases of bronchiectasis and 6 cases of chronic pharyngitis. Chronic pleurisy was present in 66 (40%) of the number; this condition is ordinarily not found in uncomplicated silicosis, but in silicosis with a complicating infection.

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CONTRALATERAL SPONTANEOUS PNEUMOTHORAX COMPLICATING ARTIFICIAL PNEUMOTHORAX.

WITH A REPORT OF TWO CASES.

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(From the Sanatorium Division of the Boston City Hospital.)

The occurrence of superimposed spontaneous pneumothorax during the course of pneumothorax treatment is not an infrequent complication, but a review of the literature shows that contralateral spontaneous pneumothorax complicating artificial pneumothorax is very rare.

Dunham[2] (1926), reported a case of spontaneous pneumothorax occurring in the contralateral lung during the course of artificial pneumothorax with complete recovery. The diagnosis was made by fluoroscopic and radioscopic examinations, the patient presenting no symptoms whatsoever. He states that prior to this date, review of the literature failed to disclose such a case on record.

Burrell[1] (1932), in a report on 671 pneumothorax cases in which a total of 10,889 punctures of the pleura were made, mentions 3 cases which developed contralateral spontaneous pneumothorax as a complication of artificial pneumothorax with fatal results.

Stephani[5] (in 1936), reported a case of contralateral spontaneous

pneumothorax complicating artificial pneumothorax, the diagnosis being made by radioscopic examination. The patient stated that he had a transitory pain in his chest a few days previously, but that there were no other symptoms. The spontaneous pneumothorax was absorbed in 3 months. The patient made a good recovery.

Over a period of 5 years, 1933–1937, covering a series of 877 pneumothorax cases in which 34,789 pleural punctures were made, we were able to find only 2 cases which developed contralateral spontaneous pneumothorax.

By a spontaneous pneumothorax, we mean a pneumothorax which is not brought about by external factors either accidentally or for therapeutic reasons.

Pulmonary tuberculosis is probably the most frequent primary cause. Other exciting factors which may produce this condition are lung abscess, gangrene, bronchiectasis, empyema, emphysema, and foreign body.

The direct causes of spontaneous pneumothorax are: 1, Rupture of an emphysematous bleb; 2, perforation of a cavity into the pleural space; 3, rupture of a subpleural tuberculous lesion.

We differentiate three types of pneumothorax. 1. In the closed type the manometer, reading reaching a certain positive pressure, remains constant, showing that no more air is entering the pleural space. 2. In the open type, the manometer reading remains constant, fluctuating from a certain positive to a certain negative pressure even after air has been aspirated. 3. In the valvular type, the manometer readings show a constantly increasing positive pressure.

Rubin[4] states that males are more often affected than females, the ratio being about 4 to 1. This is usually explained on the basis of increased effort and strain in the male.

Spontaneous pneumothorax may be complete or partial, depending upon the size of the perforation into the pleural space and presence of adhesions. The signs and symptoms presented by the patient will depend upon the following factors: 1, rapidity of onset; 2, types of pneumothorax—whether closed, open, or valvular; 3, size of perforation into the pleural space; 4, presence of adhesions; 5, amount of collapse on contralateral spontaneous pneumothorax side; 6, amount of collapse already present on the opposite pneumothorax side.

A consideration of the above-mentioned factors explains the presence of a spontaneous pneumothorax in some cases which do not complain of pain, shock, or dyspnea. The diagnosis is made in these cases by fluoroscopic and radioscopic examinations.

Case Abstracts. CASE 15,730.—J. M., white longshoreman, aged 35. *Family history:* Negative for tuberculosis. *Past history:* Pneumonia in 1928.

Patient was admitted to the Sanatorium April 23, 1937, with a 6 months'

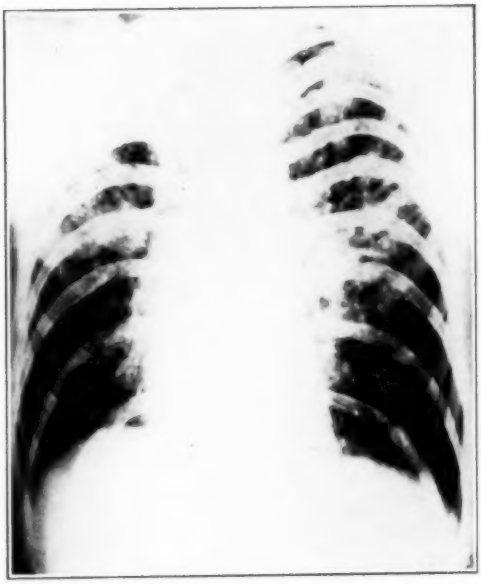

FIG. 1.—(Case 1). Roentgenogram on admission showing infiltration and cavitation of the right upper lung field and infiltration of the left mid-lung field.

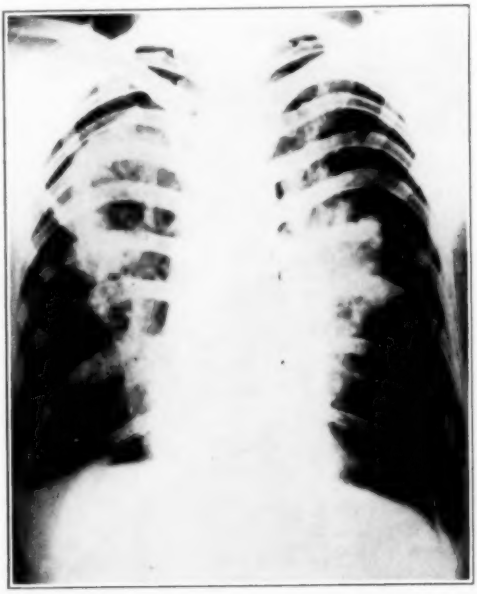

FIG. 2.—(Case 1). Roentgenogram showing partial collapse of both right and left lungs with adhesions. Spontaneous pneumothorax has occurred on the left side. Note how the cavities on the right side are brought into view after the induction of artificial pneumothorax.

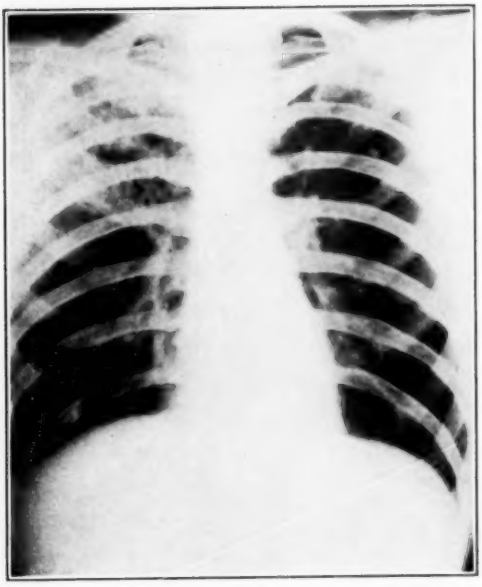

FIG. 3.—(Case 2). Roentgenogram on admission showing marked infiltration of the upper half of the right lung field with some infiltration of the left upper lobe at the periphery.

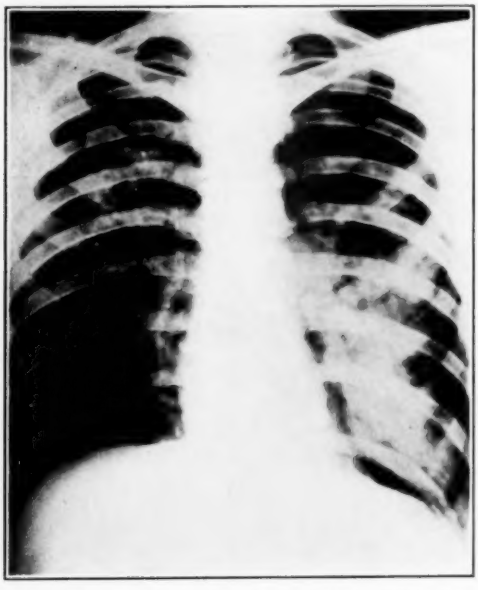

FIG. 4.—(Case 2). Roentgenogram showing partial collapse of both right and left lungs with adhesions. Spontaneous pneumothorax has occurred on the left side. Note the marked pneumonic process in the left lower lobe.

history of moderate cough and expectoration of 3 ounces yellow sputum daily; no history of streaking nor hemoptysis. Two months prior to entry he had an attack of pleurisy on the right side for which he was treated at home by his local physician.

One month before entry he began to complain of weakness, moderate dyspnea on exertion, loss of strength, loss of appetite and 26 pounds in weight (in past year), and occasional night sweats.

On admission, the temperature ranged from 97.2° to 101° F., the pulse from 80 to 110 per minute, and respiratory from 18 to 22. The sputum was positive for tubercle bacilli. Sedimentation rate 30 V. C. (Cutler Method). Weight, 114 pounds.

On examination, one noted a poorly developed and nourished, prematurely gray male, with negative physical findings except of the chest. Examination of the right chest revealed signs of infiltration over the upper half with signs of cavitation over the infraclavicular region anteriorly and supraspinatus area posteriorly. Examination of the left chest revealed signs of infiltration in the mid-lung region. Roentgenogram reports confirmed above physical findings.

The case was presented at conference, and it was the consensus of opinion that pneumothorax should be instituted on the right side. On May 3, 1937, this was begun with an initial reading of −4−7 and a final reading of −2−6 after the injection of 300 cc. of air. Refills were made twice weekly, the amounts ranging from 300 cc. to 550 cc. of air, with final readings never higher than −1−4. Frequent fluoroscopic examinations were made to check the amount of collapse, which was progressing quite favorably. Clinically, the patient showed a good deal of improvement.

On May 22, 1937, the patient developed a sudden, sharp, agonizing pain in the left chest. He was found sitting up in bed, very dyspneic, cyanotic, in profuse sweat, with a fast, thready pulse.

A quick examination of the chest showed that there was hyperresonance over the left chest with distant breath sounds. Time was not taken to localize the exact position of the heart because of the patient's poor condition. Inasmuch as there was no time to obtain a pneumothorax outfit, a standard 2-inch 15-gauge needle was inserted into the left pleural cavity, and air began to escape under pressure. The patient obtained immediate relief, and as soon as his condition improved, the needle was removed.

About 7 hours later, the patient became short of breath, and inasmuch as there was more time and the condition of the patient permitted, a pneumothorax outfit was taken to the bedside. The initial reading in the left pleural cavity was found to be +4−4. After removing 600 cc. of air, the patient was greatly relieved, and a final reading of −1−8 was obtained.

Fluoroscopic examination and roentgenogram confirmed the diagnosis of spontaneous pneumothorax on the left side.

Air was removed on 3 other occasions, the amounts ranging from 150 cc. to 400 cc.

In view of the disease in the left lung, it was thought advisable to keep a certain amount of collapse. Consequently, refills were given once weekly on the right and left sides. Negative final readings were maintained on both sides on all refills. Frequent fluoroscopic examinations were made to check amount of collapse. In spite of repeated warnings as to the seriousness of his condition, the patient persisted in taking poor treatment and continued to be uncoöperative.

On August 1, 1937, patient had a massive pulmonary hemorrhage and died. Postmortem examination could not be obtained.

Case 15,516.—W. H., male, white truck driver, aged 27. *Family history:* Negative for tuberculosis. *Past history:* Three attacks of pleurisy left side.

Patient was admitted to the Sanatorium December 7, 1936, with a

6-months' history of cough and expectoration of 2 ounces yellow sputum daily. No history of streaking nor hemoptysis.

In addition, the patient complained of marked hoarseness for the past 3 months. No dysphagia nor soreness of throat. Slight loss of appetite and loss of 13 pounds in weight in 6 months.

On admission, the temperature ranged from 97° to 99.2° F., the pulse rate from 70 to 90, and respiratory rate from 20 to 24. The sputum was positive for tubercle bacilli. Sedimentation rate 23 D. C. (Cutler Method). Weight, 132 pounds.

On examination, one noted a fairly well developed, somewhat undernourished male, in no apparent distress. His speech was markedly hoarse. With the exception of the chest and laryngeal findings, the physical examination was negative. Examination of the right chest revealed signs of infiltration most marked over the upper third with signs of cavity over the infraclavicular region anteriorly and supraspinatus area posteriorly. Examination of the left chest revealed signs of infiltration at the apical region. Roentgenogram reports confirmed the physical findings. Laryngologist made diagnosis of tuberculosis of the larynx.

The patient did fairly well on strict bed rest until April 15, 1937, when he had a hemoptysis of 5 ounces. As signs of cavitation were present on the right side in addition to its being the most diseased side, pneumothorax was instituted with an initial reading of −5−10. After injecting 600 cc. of air, a final reading of −2−6 was obtained.

Refills were given twice weekly, and this form of therapy prevented further hemoptyses, although the patient had blood-streaked sputum on several occasions. Frequent fluoroscopic examinations were made to check amount of collapse.

On June 2, 1937, patient developed a severe pain in the left chest, became somewhat dyspneic with an elevated and thready pulse. No cyanosis was present. Examination of the chest revealed hyperresonant note over left chest with distant breath sounds. No displacement of the trachea nor heart could be ascertained. Pneumothorax outfit was brought to the bedside, and needle was inserted into the left pleural space. The initial reading was +2−6. After removing 350 cc. of air, the patient was greatly relieved, and when the final reading of −2−8 was obtained, the needle was withdrawn. Fluoroscopic examination and roentgenogram confirmed the diagnosis of spontaneous pneumothorax on the left side.

No further removal of air was necessary from the left side. In view of marked pneumonic process, which had developed at the left base, it was thought advisable to keep up a partial collapse of the lung. Refills were given once weekly on both sides, the amounts ranging from 100 to 200 cc. of air, with no final reading higher than 0−8 on either side.

The patient's throat condition, despite strict silence and chaulmoogra oil treatment, became worse, with development of marked dysphagia. Patient became much weaker, due to inability to swallow anything, and expired July 23, 1937.

AUTOPSY revealed the body of a 27-year-old, emaciated, white male.

In order to confirm the diagnosis of air in the pleural cavity, a quantity of water was placed between the chest wall skin flap and the intercostal musculature. Then a stabwound was made through the water into the pleural space. Air bubbled up through stabmarks in the intercostal spaces.

Left pleural cavity: Partial collapse of the lung was seen. A firm, thick, fibrous adhesion binding the apex to the chest wall, and 2 or 3 thick adhesions at the base were present. Right pleural cavity: Lung was found to be partially collapsed. A few thick, fibrous adhesions binding the apex and one corner of the base of the lung to the chest wall were seen. The pericardial and peritoneal cavities were negative.

Left lung: Weight 980 gm. A large part of the anterior surface was covered by a thickened, dull, pigskin-like layer of fibrin. Same appearance was seen on the lateral border of the lung.

The interlobar fissure was obliterated by fibrous adhesions. The pleura was somewhat thickened, but smooth and fairly shiny. Everywhere the underlying lung was felt to be lumpy and nodular. Grayish-white nodules, 2 to 3 mm. in diameter, and conglomerations of nodules were seen beneath the pleura. Several areas about 2 cm. in diameter were easily indented by light touch. These were seen on section to be cavities beneath the pleura. The cut surface of both lobes had a grayish color and almost solid with small, grayish-white nodules about 2 cm. in diameter. There were several cavities from 0.5 to 2.5 cm. in diameter, some thick and others thin-walled, lined with shaggy necrotic membranes, and containing rather thick, yellow, purulent material. Many of these cavities connected with branches of the bronchi. There was a large, ragged cavity near the hilus in the base of the upper lobe about 3 cm. in diameter.

Right lung: Weight 900 gm. The pleura was slightly thickened over the entire lung, and smooth except under the few thick adhesions at the apex and base. Most of the lung felt lumpy and nodular to the touch.

The cut surface was grayish-red with many small, grayish-white nodules about 2 mm. in diameter. Heavy strands of white, fibrous tissue extended throughout the upper lobe, replacing much of the lung substance. There were a few cavities of 0.5 to 1.5 cm. in diameter in the upper lobe containing grayish-green, purulent material.

The bronchial branches in the middle lobe were dilated terminally. The lower lobe contained many nodules, a small amount of fibrous tissue, and a few small cavities. The bronchial mucosa was moderately congested. The bronchi contained a small amount of gray, mucopurulent material.

The rest of the postmortem examination was essentially negative with the exception of the larynx, where 3 shallow ulcers were found on its posterior aspect.

Anatomic Diagnosis: Left pneumothorax. Right pneumothorax. Bilateral fibrocaseous pulmonary tuberculosis with cavitation. Old fibrous pleuritis. Bronchiectasis of right middle lobe. Tuberculosis of the larynx.

What effect the presence of artificial pneumothorax had in the production of the contralateral spontaneous pneumothorax is difficult to say.

Matson, Matson, and Basaillon,[3] among others, have pointed out that the end results of pneumothorax therapy are less dependent upon the status of the contralateral lung than they are upon the character of the collapse and the type of disease in the more diseased lung.

There is no doubt that the contralateral lung is forced to more activity when the opposite lung is undergoing collapse therapy.

We are of the opinion that the presence of artificial pneumothorax merely hastened the contralateral spontaneous pneumothorax. In all probability, the condition may have occurred even without the presence of artificial pneumothorax on the one side.

Summary. 1. Considering the number of artificial pneumothoraces that are performed today, it is surprising to see the rare occurrence of contralateral spontaneous pneumothorax as a complication of artificial pneumothorax. Review of the literature reveals 5 such cases.

2. In our series of 857 pneumothorax cases in which 34,789 pleural punctures were made, only 2 cases developed the condition.

3. A report of the 2 cases is presented with postmortem findings on 1.

4. The complication may not in itself be fatal if the condition is diagnosed early enough and proper treatment instituted.

5. We believe that it is advisable to keep a certain amount of collapse on the contralateral spontaneous pneumothorax side if the lung shows evidence of disease by past physical examination and roentgenograms. On the other hand, if the lung is normal, then it may be allowed to reëxpand.

6. Frequent manometric readings and fluoroscopic examinations are of the greatest importance in these cases.

I am grateful to Dr. John A. Foley, Chief of Staff, and members of the Staff for valuable information rendered in preparation of this paper.

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THE RÔLE OF CERVICAL NERVES IN FACIAL SENSATIONS AND THE QUANTITATIVE DISTURBANCE OF SENSITIVITY IN MAJOR TRIGEMINAL NEURALGIA.*

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In the light of our present knowledge it seems almost unbelievable that only 125 years have passed since Bellingeri[2] first questioned the belief, then held, that the facial and the trigeminal nerve shared equally in the sensory as well as in the motor innervation of the face. This question remained unanswered until Bell[1a,b] published his brilliant experiments in 1821. He sectioned in a donkey the fifth nerve on the one side, the seventh on the other side, at their entrance into the face, and demonstrated that the face lost its sensitivity on the side of the first operation, its motility on the side of the second. One year later Fodéra[5] confirmed this observation, dividing the root of the fifth nerve close to the brainstem, a procedure to which Magendie[9] did not fail to affix his name in the following year. With these investigations the fundamental question of the sensory innervation of the face was answered.

* Read before the Philadelphia Physiological Society, February 21, 1938.

Since then new problems have arisen which still call for solution. Some of them are especially important to neurologists and neurosurgeons because of the practical consideration incident to the diagnosis and treatment of major trigeminal neuralgia. Important among these are the degree of overlap between the cervical and trigeminal nerves and the possible responsibility of the cervical nerves for the residual sensibility of the face after section of the trigeminal nerve.

A few years after having completed his first series of extirpation of the Gasserian ganglion, Fedor Krause[8] reported that in some of his patients a certain degree of tactile sensitivity was present in the face although pain sensation was gone. Cushing[3] questioned the complete removal of the ganglion, whereupon Krause deposited the intact ganglion on the speaker's table asking where, in Cushing's opinion, should the fibers run which should account for the preserved touch sensation.

This lively controversy provoked careful investigation in two directions. Zander[11] and Frohse[7] traced the terminal ramifications of the nerves emerging from the cervical roots into the face, using gross anatomic methods. Zander demonstrated that the filaments of the cervical nerves were present in all but the central portion of the face. This small central area represents what we call the pure trigeminal field. In addition, Frohse[7] showed that a considerable degree of variability existed in the territories supplied by each division of the fifth nerve and by the cervical segments. Cushing,[3b] on the other hand, using horse hair, pin and the faradic current, examined the cervico-trigeminal borderline and found here that Sherrington's law of overlap was not valid, at least not to its full extent. Sherrington had proved that every territory of the body was innervated by three posterior roots and that destruction of any one of them produced almost no loss of sensibility. In contrast to this fact, Cushing[3a] showed that section of the fifth nerve as well as of the cervical roots produced a complete anesthesia of the corresponding fields which were mutually complementary; that is with the methods available at that time. In the monkey, however, Sherrington[10] was able to demonstrate a considerable cervico-trigeminal overlap, using his method of residual sensibility. The situation is complicated still further by Dandy's[4] claim that by cutting four-fifths of the trigeminal root close to the medulla touch sensation may be largely preserved over the face though sensation of pain is lost.

Although all these problems urgently required solution, no attempt has been made in the last 20 years to attack them with the tools of contemporary neurophysiology.

The material presented here was based on 50 patients suffering from major trigeminal neuralgia. They were examined repeatedly on the normal and abnormal sides and on the latter both before and

after subtotal resection of the trigeminal sensory root with v. Frey's graduated hairs and thorns and Head's algesimeter. In addition, threshold and excitation time to electrical stimulation were determined both for touch sensations (described as similar to a knock) and for short pain sensations. Condenser discharges and electrodes of 1 or of 10 mm. diameter were employed. The smaller electrode was applied directly on the touch or pain points. With the latter, 513 determinations of the threshold and 929 of the excitation time provide sufficient material for statistical treatment. Ten normal persons served as additional controls.

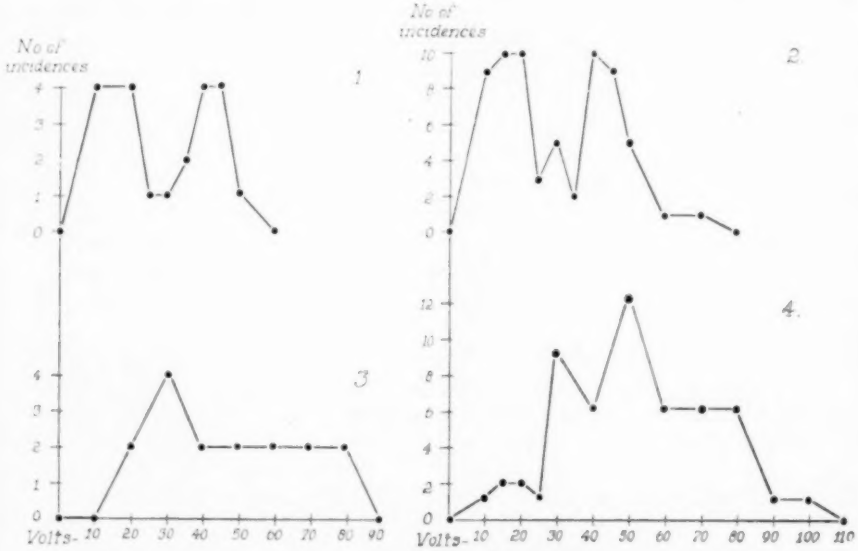
Two factors hindered the evaluation of this large mass of material. Although the surgeon attempts to divide just those fibers of the trigeminal root that supply the aching portion of the face, there is no accurate way of knowing whether he may not have destroyed a greater or lesser number of fibers in a given patient. The other source of perplexity is connected with the observation that even in normal individuals the threshold readings of adjacent touch points within a 1 sq. cm. area of the same peripheral division varies from 1 to 5 milliampères during an examination.

For these reasons, I preferred to disregard single patients for the time being and to treat my material collectively with mathematical methods, hoping to find a common denominator. Frequency curves were drawn, plotting the *threshold values of touch points* on the abscissa against the number of incidences on the ordinate. The first graph (Fig. 1) shows the figures resulting from electrical stimulation of the touch points within an area of 4 sq. cm. in the second division of the fifth nerve on the normal side of a person suffering from trigeminal neuralgia. Figure 2 represents the aggregation of values from all three trigeminal divisions in 10 normal individuals. Both these curves are similar in their general characteristics. They show two maxima, one between 15 and 20 volts, the other between 40 and 45 volts. The corrected standard deviations for the mean values of 17.5v and 41.3v are 6.9 and 7.1 respectively, with a significant difference between the two coefficients of variation. The frequency relation between the incidence of these two values is approximately 1:1 in the first and second division of the fifth nerve, but 1:2 in the medial portion of the third division, and 1:3 in its external part.

At first glance the presence of two maxima seems astonishing but this is not entirely unprecedented. Franz[6] examined the face of normal persons with v. Frey's hairs and found that 50% of the touch points were detectable with hairs of 0.081 gm. while the rest required 0.24 gm. for detection. I resorted to this method to find out whether the above mentioned distribution of touch points could be confirmed in single persons. Not more than 4 persons were available for study, on whom the result could be considered reliable. Itching and after-sensations in a short time became so disturbing that they often

prevented a certain discrimination between the real sensation and the associated dysesthesias. In these 4 persons one-half of the touch points were elicited with hairs of ½ gm./mm.² the other half with hairs of 1 gm./mm.² over the forehead and cheek, while over the medial portion of the third division the ratio was 1 to 2, and over its lateral part 1 to 5.

These examinations suggest that the touch points of the face have no uniform threshold, but that the majority fall into two groups, one with electrical threshold of 1.5 ma and 15 volts and the other



Figs. 1 to 4.—Frequency curves of rheobases of the first knocking sensation before and after subtotal retrogasserian neurotomy.

Fig. 1.—From the normal side of the face of a patient with trigeminal neuralgia.

Fig. 2.—From 10 normal persons.

Fig. 3.—From the pathologic side of the face of the same person as in Fig. 1 after subtotal retrogasserian neurotomy.

Fig. 4.—Postoperative mean values of 53 persons after subtotal retrogasserian neurotomy. Figs. 3 and 4 show the loss of the first peak of the frequency curve after subtotal section of the fifth nerve root.

with one of 3.5 ma and 40 volts. These findings are constant whether one examines a single division of the fifth nerve or the whole face, whether a single person or a group of persons. However, the two kinds of touch points are equally distributed only in the area of the first and second trigeminal divisions, whereas the number of points with higher threshold increases as we approach the outer part of the third division and the cervical segments.

From the data it appears that the higher values are more frequently found in the sensory areas where branches of cervical nerves

are likely to be most numerous while the lower values are largely confined to the trigeminal system. If this hypothesis should hold true, the frequency curves, after section of the fifth nerve, should lose their first peak. This is found to be the case. Figure 3 shows the postoperative frequency curve of the same patient whose preoperative curve was given in Figure 1. Figure 1 represents the normal side. However, the abnormal side was not significantly different before operation. Figure 4 corresponds to Figure 2 and depicts the frequency of incidence of 53 postoperative threshold determinations in a number of patients. Both these curves plainly show that the maximum at 15v has disappeared while the maximum around 40v is still present.

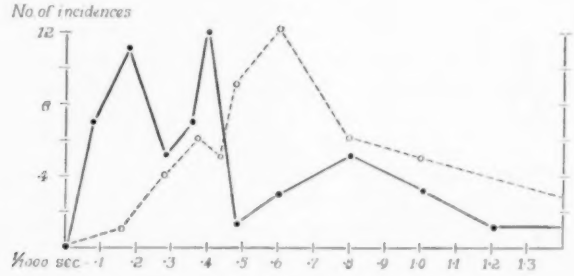


FIG. 5.—Frequency curves of the chronaxie of touch sensation before (———) and after (– – – –) subtotal retrogasserian neurotomy. Loss of the first peak of the frequency curve after operation.

Accordingly, the touch points with a low mechanical threshold always disappear after subtotal section of the fifth nerve root, while those with a threshold of 1 gm./mm.^{2} and more are present as a rule.

Briefly, there are *two sets of touch points in the face*, distributed in a definite mutual relation per square centimeter within the area of the three trigeminal divisions. One set has a mechanical irritability of $\frac{1}{2}$ gm./sq. mm. and a corresponding rheobase of 15v, the second has a threshold of 1 gm./sq. mm. and rheobase of 40v, central mean value, respectively. *After subtotal section of the fifth nerve root, the first group has more or less disappeared while the second remains unaltered.*

Turning from the mechanical and electrical threshold to the *time factor of touch sensation*, we find again the double peaked frequency curve (Fig. 5). The central mean of the two maxima is situated at 0.2 milliseconds and 0.4 milliseconds, respectively, in normal persons. After subtotal retrogasserian neurotomy, the figures at 0.2 milliseconds disappear, the values around 0.4 milliseconds remain and a new maximum appears at 0.6 milliseconds. This may mean a shift of the two maxima to the right. Or we may assume that those touch fibers which have escaped the section changed their chronaxie from 0.2 milliseconds to 0.6 milliseconds. One factor

definitely stands out, the maximum at 0.2 milliseconds has disappeared after root section as did the threshold values at 15v.

This is not so with *pain sensations*. The frequency curve of the time factor to a sharp sensation in normal persons has only one maximum. The central mean is found around 1.2 milliseconds in the distribution of the fifth nerve proper, and at 2.4 milliseconds in the lateral region of the third division where it borders on the cervical segments. After retrogasserian neurotomy these figures go up to 0.4 milliseconds and 0.8 milliseconds, respectively, at the points where pain sensations are preserved.

The greater uniformity of the irritability of the pain points in the normal face is also confirmed by their mechanical threshold. Thorns applied with $\frac{1}{4}$ gm. are adequate to stimulate 75% of all pain points in the areas of the first and second divisions of the trigeminal nerve and over the chin, 50% in the medial portion of the third division, and 20% in its lateral part. The remainder required $\frac{1}{2}$ gm.

The marked difference in the behavior of touch and pain sensation in the face following subtotal division of the trigeminal root is illustrated by the frequency of a total loss of each of the two sensations. Not more than 25% of our patients showed complete loss of touch sensation, but 77% loss of pain sensation in the second and third divisions. In other words:

1. In the region affected by the neurotomy, *painful sensations cannot be elicited in about three-fourths of the examined patients*, either mechanically or by currents of 25 ma and 250v. If a threshold exists, pain could not be produced unless electrical stimulation exceeded $\frac{1}{3}$ second duration.

2. The *frequency of a total loss of time excitability to a sharp sensation is 50% greater than to a knocking sensation.*

The clearest conception of the irritability of the sensory nerve fibers in the face in normal and neuralgic individuals as well as in persons after subtotal retrogasserian neurotomy, will be gained from surveying Table 1. The figures in this table indicate the *quantity of electricity in microcoulombs required to produce a touch or pain sensation*. The table shows that trigeminal neuralgia barely changes the irritability of the touch points while the irritability of the pain points is decreased in the most frequently attacked second and third division. The adjacent areas of the major auricular nerve are hyperalgesic. After subtotal root section a considerably greater stimulus is necessary to produce a touch and a pain sensation in the preserved sensory end organs. The fact that in this instance the larger electrode requires comparatively more current than the punctiform electrode—because of the smaller number of lines of force per sense organ—suggests that we are dealing with an absolute loss of pain points—penesthesia—in addition to an increase of threshold in those points where sensation is preserved—hypalgesia. Examination with graduated thorns confirm this assumption. An

alternate hypothesis to a change in threshold is that after operation only those points which originally had a high threshold retain their sensitivity.

TABLE 1.—THE QUANTITY OF ELECTRICITY IN MICROCOULOMBS REQUIRED TO PRODUCE A SENSATION.

	Diameter of electrodes, mm.	Touch.			Pain.		
		Normal side.	Neuralgic side.		Normal side.	Neuralgic side.	
			Preop.	Postop.		Preop.	Postop.
Forehead	1	3	2·4	19			
	1	16	16	16	30	30	160
	10	16	16	24	80	64	160
Cheek	1	3	3	53			
	1	16	19	28	48	72	280
	10	19	24	75	160	100	1850
3d division	1	3	3	24			
	1	16	16	16	48	96	160
	10	24	32	320	200	320	1600
Chin	1	3	4·2	27			
	1	16	24	16	38	48	320
	10	19	24	110	160	200	
Auric. mgn.	1	6					
	1	20	18	20	120	36	200
	10	40	39	82	200	100	1600

It has been explained above that after extirpation of the Gasserian ganglion a certain degree of tactile sensibility may be preserved. Conversely, we have examined patients in whom no sensitivity has returned for a longer period in the medial part of the face after a section of the fifth nerve root which was intended to be subtotal. The varying size of the completely anesthetic area seems to coincide with the extent of the beard free space. The assumption that tactile fibers from the lower part of the face, showing the functional characteristics of cervical filaments, may run over the fifth nerve is consistent with the anatomic facts.

I shall demonstrate elsewhere that the comparison of the healthy with the neuralgic side of the face in a patient with trigeminal neuralgia may occasionally show quantitative deficiencies in sensitivity, helpful in the problems of differential diagnosis. The small deviation from the normal in sensitivity over the neuralgic side of the face in a statistical treatment of the figures found in a large group of patients suggests, in my opinion, that *a quantitative change of sensibility*—implying a lesion of the trigeminal nerve and its ganglion—*is a contributory rather than an essential factor in the mechanism of neuralgia of the face.*

Summary. 1. The normal sensibility of the face was tested in 10 normal subjects and in 50 patients with unilateral trigeminal neuralgia. In the latter, tests were also made on the pathologic side both before and after subtotal section of the fifth nerve root. Five hundred and thirteen electrical determinations of threshold and 929 of excitation time both for touch and pain sensation were

treated with statistical methods. In addition, tests were made with graduated hairs and thorns.

2. Frequency curves, in which the threshold values of the touch points in volts are plotted against the number of incidences, show two maxima, the one at 15v, the other at 40v. After section of the fifth nerve root, the maximum at 15v disappears while the maximum at 40v remains unchanged.

3. Frequency curves of the time factor of touch sensations show a similar two-humped curve. The first of these two peaks disappears after section of the fifth nerve root.

4. The two sets of touch points are distributed in a definite mutual relation per square centimeter in the three areas supplied by the trigeminal divisions. Their ratios are 1:1 in those of first and second division; 1:2 in the medial area supplied by the third division, and 1:3 in the lateral part.

5. It is inferred from these observations that the touch points having a low mechanical and electrical threshold and a low time factor are innervated by the fifth nerve, those having high values are supplied by the cervical segments, while the pain points are supplied by the fifth nerve only.

6. The cervical segments overlap with their touch fibers the territory of the fifth nerve in the face with the exception of its most medial region.

7. The frequency curve of the time factor to painful stimuli has only one maximum. The majority if not all pain points within the area of the fifth nerve proper seem to be supplied by the fifth nerve. After retrogasserian neurotomy 75% of all patients suffer a complete loss of pain sensation, but only 25% a complete loss of touch sensibility.

8. In patients with trigeminal neuralgia the irritability of touch points over the neuralgic side of the face is not changed, the irritability of the pain points is slightly decreased. A quantitative change of sensibility in the face seems not to be an essential factor in the mechanism of neuralgia of the face. The peripheral nerve and its ganglion, therefore, are probably not the chief location of the lesion in trigeminal neuralgia.

9. The disturbance of sensibility after subtotal section of the fifth nerve root is characterized by a complete disappearance of some pain points—penalgesia. Those points that remain show a high threshold—hypalgesia. Either their threshold has been raised or only those points of abnormally high threshold have survived.

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PATHOLOGIC CONSIDERATIONS OF THE THORACIC DUCT.*

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The thoracic duct has received comparatively little attention in the American literature. This, probably, is attributable to the rarity of conditions affecting it, its inaccessibility anatomically, and lack of interest in investigating its relation to disease in human beings. This study was undertaken to determine the incidence and type of conditions which affect it.

Methods of Study. The material on which this study is based was derived from 119 consecutive necropsies performed at The Mayo Clinic in 1937 and from reports of necropsies during the period 1929 to 1937. From the latter source, 3 cases of disease of the thoracic duct were selected because histologic sections or gross specimens were preserved and available for examination.

The thoracic duct was approached from the thoracic aspect of the structure above the diaphragm. It was isolated, followed downward from the thorax, the cisterna chyli identified when possible, and the principal trunks emptying into the duct were dissected free. Any closely adherent lymph nodes were dissected out together with the trunks and cisterna chyli and were included in the structures removed. In most cases, it was impossible to follow the duct through the thorax and neck to the junction with the venous angle owing to limitation of the necropsy incision in the neck. It was followed as far cephalad as possible and was removed as a whole. Injection of the duct was not carried out owing to the delicacy of the wall in fresh tissue, and because injection would force out any material such as carcinomatous cells, blood, or other cellular structures which would be of interest in a study of this type. In most cases, as much as possible of the surrounding fibrous and adipose tissue was included in the dissection in order to make larger blocks for imbedding and cutting, and to include interesting lymph nodes or inflammatory tissue in the periductal structures.

After removal, the duct was placed in 10% formalin for 24 hours before blocks were cut for histologic sections. Representative cross-sections were cut from various levels of the cisterna chyli and thoracic duct, imbedded in paraffin, cut, and stained with hematoxylin and eosin. Gram stains of the tissues were made when indicated.

Report of Cases and Findings at Necropsy. The following 12 cases were found in which there was involvement of the thoracic duct by a pathologic process. In Cases 1, 2, and 3, suppuration of the

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thoracic duct and cisterna chyli were discovered at necropsy. In Cases 4, 5, 6, 7, and 8, carcinoma was found involving the cisterna chyli or thoracic duct. In Cases 9, 10, and 11, thrombosis of blood was found in the duct, and in Case 12, perilymphangitis of the thoracic portion of the duct was found.

CASE 1. The patient was a white man, aged 30. The chief complaints were diarrhea, occasionally bloody, for 1 year; loss of weight and strength during the last 6 months; nocturnal edema of the ankles for the past 3 or 4 weeks. Examination at home revealed diffuse polyposis of the colon. Examination at the clinic confirmed this diagnosis and roentgenologic examination revealed a filling defect suggestive of carcinoma in the descending portion of the colon. There were cardiac findings suggestive of bacterial endocarditis and repeated blood cultures revealed hemolytic streptococci. The patient's course in the hospital was marked by a septic type of fever, a stuporous and irrational mental condition, and a steadily downhill course. Death occurred on the 17th day after admission.

Findings at Necropsy. At necropsy, the significant findings were polyposis of the colon with carcinomatous change, ulcerative vegetative endocarditis of the mitral and aortic valves, acute diffuse nephritis, multiple infarcts of the spleen and kidneys, multiple abscesses of the cardiac muscle, multiple infarcts and abscesses of the brain, infarcts of the lungs, and multiple abscesses of the periaortic lymph nodes. The thoracic duct and cisterna chyli were markedly dilated, reddish-yellow in color, and surrounded by large, red, soft lymph nodes. The cisterna measured 2.5 cm. in diameter. The thoracic duct varied in diameter throughout its course, ranging from 1 to 0.5 cm. The duct entered the left subclavian vein at the junction of that vein with the left internal jugular. On cutting through the cisterna after fixation in formalin for 24 hours, a yellowish-pink material, semiliquid in consistency, coiled out. There were several enlarged lymph nodes adherent to the cisterna and its large trunks. Histologic sections of the cisterna revealed the following: the walls were infiltrated with neutrophils and there was marked degeneration and narrowing of the muscularis. The endothelial lining was indistinct. The lumen was occupied by a mass of fibrin, leukocytes, and endothelial cells. At one point, the thrombus and wall of the cisterna chyli were intimately associated by means of fresh fibrous connective tissue. There was marked leukocytic infiltration of the surrounding connective tissue. A lymph node adjacent to the cisterna contained several nodules of metastatic carcinomatous cells. The lymphoid tissue of the nodes was hyperplastic. Sections made through the cervical portion of the thoracic duct revealed the same picture of thrombosis and suppuration. Gram stains of the sections disclosed Gram-positive cocci in short chains resembling streptococci (Fig. 1).

This patient died of sepsis incident upon bacterial endocarditis with multiple infarction of almost every organ in his body. In addition, he had polyposis of the colon with carcinomatous change in several regions which probably antedated the bacterial endocarditis. There were abscesses in the periaortic nodes and these nodes drain directly into the radicles of the cisterna chyli; it is possible that the source of infection in the thoracic duct was the abscessed nodes. The lymphatics of the colon drain to the mesenteric and, thence, to the periaortic or lumbar nodes. Ulceration and formation of abscess in polyps or carcinomas of the colon are not uncommon and this condition might have served as the original focus of infection

leading to suppuration in the thoracic duct. From the duct, the organisms pass readily into the blood stream and it is probable that this was the route of infection leading to vegetations on the valves of the heart.

CASE 2. The patient was a white man, aged 59. The chief complaints were pyrosis and eructation for 5 years, cramping pain across the upper abdomen for 2 years, and fever, night sweats, nausea, vomiting, and pain in the umbilical region for the past 3 weeks. Examination revealed moderate emaciation, jaundice, and enlargement of the liver. Laboratory studies disclosed sugar in the urine, elevation of the serum bilirubin, and a nonfunctioning gall bladder was discovered by cholecystography. He was admitted to the hospital at once and his course there was marked by severe chills and fever, progressive elevation of the blood urea, a decreasing urinary output, and, terminally, cyanosis and coma. Death occurred before surgical relief could be attempted.

Necropsy. Necropsy revealed carcinoma of the head of the pancreas with necrosis and formation of abscess. There was a fistulous communication between the pancreas and duodenum and between the pancreas and common bile duct, multiple abscesses of the periaortic lymph nodes and thoracic duct, and marked bilateral pyelonephritis. The wall of the cisterna chyli and lower portion of the thoracic duct was necrotic. Histologic sections of the cisterna and duct revealed marked necrosis of the wall, infiltration of the surrounding tissues by neutrophils, and the endothelial lining of the duct was replaced by masses of bacteria which stained deep blue with hematoxylin.

The source of infection, in this case, was an abscess and necrosis of the pancreas with involvement of the periaortic lymph nodes. These nodes, in turn, led to infection of the thoracic duct. Blood cultures were not taken, but it is likely that they would have been positive because the thoracic duct was not occluded and organisms had ready access to the general circulation.

CASE 3. The patient was a white man, aged 51. The chief complaints were epigastric pain and distress after meals for 35 years. These symptoms began after the swallowing of lye. They were relieved by soda or milk. The last episode of distress began 3 weeks before admission to the clinic and was not relieved by alkali or milk. Examination revealed moderate epigastric tenderness and marked anemia. Surgical exploration after preparation of the patient disclosed a subacute perforating ulcer in the pylorus for which posterior gastro-enterostomy was performed. The postoperative course was stormy, marked by bilateral bronchopneumonia and pleural effusion. There was progressive failure and death occurred on the 10th postoperative day.

Necropsy. At necropsy, there was found edema of the lungs and bronchopneumonia. The only other finding of significance was chronic suppuration of the thoracic duct and cisterna chyli. There was a small abscess in one of the periaortic lymph nodes. There was pus in the cisterna, in its large branches, and in the thoracic duct throughout its course. The tissue surrounding the duct was indurated and there was evidence of inflammation. Histologic examination of the thoracic duct revealed necrosis and leukocytic infiltration of the wall of the organ and the lumen was filled with neutrophils. The surrounding areolar tissue also was infiltrated with leukocytes **(Fig. 2).**

In this case, as well as in the 2 previously reported, suppuration of the cisterna chyli and thoracic duct was associated with forma-

tion of abscess in the periaortic lymph nodes which drain directly into the cisterna chyli by way of the large lymphatic trunks. It is likely that, in this case, infection followed surgical operation and led to formation of abscess in the periaortic node. From the abscess in the node, infection spread through the lymphatic trunks to the cisterna chyli and thoracic duct and from the general circulation affected the lungs, thus leading to pneumonia.

CASE 4. The patient was a white woman, aged 65. The chief complaint was of a tender nodule in the right breast with redness of the overlying skin, first noticed 10 months previously. Seven months previous to coming to the clinic, intensive deep Roentgen therapy was given. Cough developed during the course of these treatments, but disappeared in 2 months. For the preceding 3 months a small, painful mass had been present over the right second costosternal junction. Examination revealed dimpling and slight retraction of the nipple of the right breast and there was a firm mass 3 by 5 cm. in extent beneath the skin in the upper outer quadrant. The right axillary nodes were enlarged and there was a tender mass near the right second costosternal junction. Roentgenologic examination of the chest disclosed old fibrous tuberculosis with cavitation in the right upper lobe with extension to the right lower lobe. There was no metastasis evident in the thorax. Radical amputation of the right breast was performed. On the 14th postoperative day cough and dyspnea developed. Roentgenologic examination of the thorax at the bedside gave evidence of fluid on the right side and evidence of carcinomatous metastasis in the right hilus. Aspiration of fluid from the right pleural cavity controlled the effusion. The fluid was brown in color, cultures were negative, and cytologic examination revealed no carcinomatous cells. The patient gradually failed and there was increasing dyspnea and elevation of the pulse rate. Death occurred 53 days after operation.

Necropsy. At necropsy there was found hemothorax on the right side, acute seropurulent pericarditis, residual carcinoma in the anterior part of the mediastinum and in the first and second ribs on the right, in the left axillary nodes and hilus of the right lung. The cisterna chyli and thoracic duct appeared normal grossly, but the surrounding connective tissue in the thoracic portion was indurated and hemorrhagic. Sections through the thoracic portion of the duct revealed carcinomatous cells invading the wall and appearing as nests of cells in the muscularis (Fig. 3).

This patient gave evidence of extensive carcinoma of the mediastinal structures secondary to carcinoma of the breast. The malignant process had spread through the pleura to invade the retropleural tissues and the thoracic duct was involved by direct extension.

CASE 5. The patient was a white man, aged 77. The chief complaints were recurrent epigastric distress 1 to 2 hours postprandially, occurring at intervals for the part 20 years. For 5 months there had been progressive anorexia and loss of 45 pounds. For the past 3 weeks vomiting of coffee-ground material after meals had occurred. Examination revealed a palpable mass in the right upper quadrant of the abdomen below an enlarged liver. Roentgenologic examination of the stomach disclosed an obstructing lesion at the outlet of the stomach. On surgical exploration this mass was found to be an inoperable carcinoma situated at the pyloric end of the stomach and had perforated into the pancreas and liver. On the 5th day, postoperatively, there appeared signs of bronchopneumonia. His condition became progressively worse and death occurred on the 6th postoperative day.

Necropsy. At necropsy there was found carcinoma of the gall bladder with obstruction of the pylorus, invasion of the liver, and metastasis to the liver, regional lymph nodes, and hepatic flexure of the colon. There was extensive bronchopneumonia and beginning empyema. The thoracic duct and cisterna chyli were not grossly affected, but histologic examination of the cisterna chyli and abdominal portion of the thoracic duct revealed carcinomatous cells invading the wall of the cisterna and replacing the endothelial lining of that vessel. There were masses of carcinomatous cells in the lumen of the cisterna not attached to the wall.

Case 6. The patient was a white man, aged 64. On admission to the clinic the diagnosis of carcinoma of the stomach was made. His condition was very poor and he was hospitalized at once. Before any examinations could be carried out he went into shock and died suddenly.

Necropsy. At necropsy there was found carcinoma of the stomach with metastasis to the liver, periaortic lymph nodes, and nodes surrounding the cisterna chyli. No cause was found for his sudden collapse and death. The thoracic duct was completely obstructed by the enlarged lymph nodes compressing it and there was 1000 cc. of chylous fluid in the peritoneal cavity. Histologic examination of the cisterna chyli and thoracic duct revealed no invasion of these vessels, but one of the large trunks adjacent to a carcinomatous lymph node was infiltrated by carcinoma which had replaced the endothelium.

In the last 2 cases, carcinoma had invaded the lymphatic vessels and had formed an epithelial lining of high columnar cells replacing the normal flat endothelium. In addition, the abdominal portion of the duct and the cisterna were encroached upon to the extent that the flow of lymph was obstructed and chylous ascites developed.

Case 7. The patient was a white man, aged 64. The chief complaints were loss of weight, pain in the epigastrium, and vomiting of the obstructive type. Examination disclosed marked emaciation and enlargement of the liver. Roentgenologic examination of the stomach gave evidence of an obstructing lesion at the pylorus. At surgical exploration, there was found carcinoma of the pylorus with metastasis to the liver and regional lymph nodes. The patient died suddenly on the 2d postoperative day, of pulmonary embolism.

Necropsy. At necropsy, the diagnosis of pulmonary embolism was confirmed; the iliac veins were thrombosed and, apparently, served as the source of embolism. There was extensive carcinoma of the pylorus with

Legends for Figs. 1, 2, 3 and 4.

Fig. 1.—(Case 1.) The wall of the thoracic duct in the upper mediastinum is infiltrated with leukocytes and the lumen is occupied by a thrombus of fibrin and leukocytes. Brown Gram stains reveal Gram-positive cocci in chains in the thrombus. There is considerable reaction in the periductal tissues, manifested by leukocytic infiltration. (× 21.)

Fig. 2.—(Case 3.) The wall of the thoracic duct is markedly thickened by replacement of muscle by fibrous tissue and there is neutrophilic infiltration of the wall. The lumen is occupied by a canalized thrombus consisting of necrotic débris, fibrin, leukocytes and bacteria. The periductal connective tissue shares in the chronic inflammatory process. (× 25.)

Fig. 3.—(Case 4.) A large lymphatic trunk adjacent to the cisterna chyli shows carcinomatous invasion of its wall. The carcinomatous cells stain deeply and stand out from the surrounding muscular tissue. (× 85.)

Fig. 4.—(Case 10.) This section was taken from the thoracic duct in the upper mediastinum and shows the thoracic duct occupied by a fresh thrombus similar to that seen in the cisterna chyli in Fig. 2. The lymph node adjacent to the duct shows Hodgkin's disease. (× 24.)

Fig. 1

Fig. 2

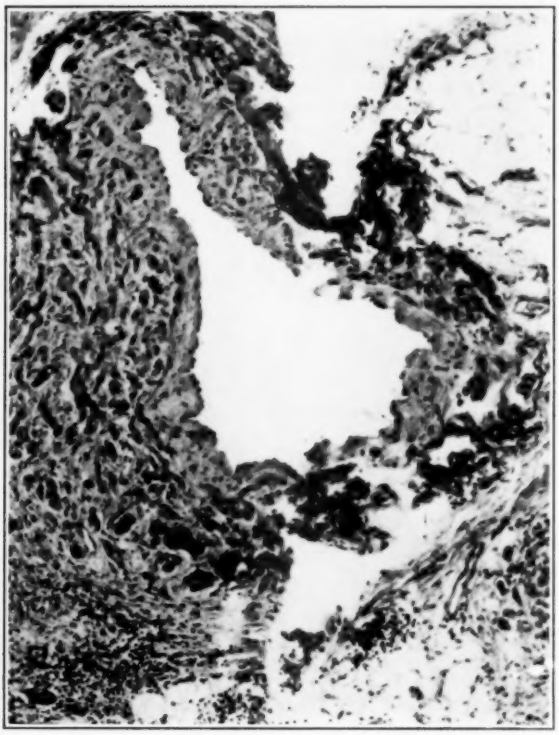

FIG. 3

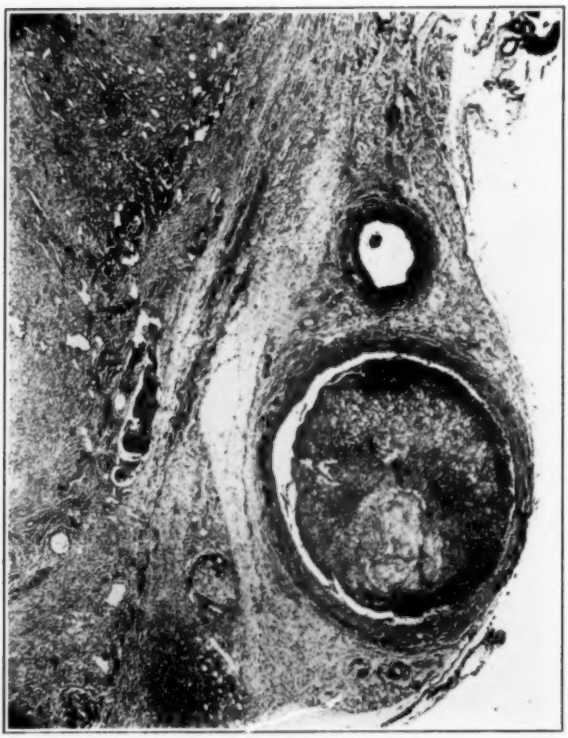

FIG. 4

metastasis to the regional lymph nodes, liver, and thoracic duct. There was extensive infiltration of the periductal tissues also, but no sign of obstruction was present. Histologic examination of the duct disclosed infiltration of the wall with carcinoma and almost complete obliteration of the lumen.

This patient, in spite of marked obstruction of the lumen both from within and without, had no signs of lymphatic stasis. It is likely that there was adequate collateral circulation of lymph and anomalous connections with the venous system so that chylous effusion was prevented.

CASE 8. The patient was a white woman, aged 68. The chief complaints were of recurrent attacks of severe right upper quadrant pain projected toward the intrascapular region, jaundice for the past 2 weeks, and fever at high as 102° F. (38.8° C.). Examination revealed mild icterus and a palpable mass in the right upper quadrant of the abdomen. Roentgenologic examination gave negative results except for elevation of the right leaf of the diaphragm. At surgical exploration, there was found metastatic carcinoma of the liver and multiple calculi in the gall bladder. The patient did well until the 12th postoperative day when signs of fluid were discovered in both pleural cavities. Despite repeated aspiration of the fluid there was steady failure and death occurred on the 31st postoperative day.

Necropsy. Necropsy revealed carcinoma of the tail of the pancreas with metastasis to the liver, lungs, diaphragm, lymph nodes, and heart. There was a thrombus composed of a mass of tumor in the hepatic vein. The gall bladder was chronically infected and filled with calculi. The cisterna chyli and thoracic duct were grossly normal, but histologic examination of the cisterna revealed a minute collection of carcinomatous cells in the lumen. The walls of the cisterna were not affected by the malignant process.

In this case the only carcinoma found in the thoracic duct was a small embolus in the lumen. It is possible that carcinoma may be disseminated in this way to reach the heart and lungs, although, in this case, carcinoma in the hepatic vein appeared to be the more likely explanation of spread from the abdominal cavity.

CASE 9. The patient was a white man, aged 44. The chief complaints were vague abdominal distress for the past 25 years, an episode of marked weakness diagnosed as anemia 5 weeks before admission to the clinic, followed in a few days by severe pain in the right lower quadrant of the abdomen, severe diarrhea for the past 2 weeks, accompanied by the passage of dark blood, and fever daily for the past 2 weeks. Examination disclosed a firm, nodular mass in the right lower quadrant of the abdomen. Roentgenologic examination gave evidence of signs of ulcerative ileitis with a granulomatous formation and the presence of a large mass extrinsic to the cecum. At surgical exploration, the terminal ileum, ascending colon, and part of the transverse colon were resected for ulcerated, annular, perforated carcinoma of the cecum with involvement of the regional lymph nodes and right ureter. The postoperative course was remarkably good for 8 days when jejunostomy had to be performed because of ileus. The following day, intermittent hemorrhages from the large bowel began and death occurred on the 11th day postoperatively.

Necropsy. At necropsy, there was found retroperitoneal hemorrhage, resolving fibrinous peritonitis, and right hydronephrosis. The cisterna chyli and thoracic duct appeared normal, grossly. Histologic examination of sections taken through the cisterna revealed a large, fresh thrombus with lymphocytes scattered about occupying the lumen of the cisterna.

Why blood should occupy the cisterna and thoracic duct is difficult to explain by anatomic dissection. It may be that retroperitoneal hemorrhage with effusion of blood into the lymph spaces and vessels causes a flow of blood through normal lymph-bearing trunks into the cisterna where thrombosis occurs.

CASE 10. The patient was a white man, aged 25. The chief complaints were of chills and fever intermittently for the past 3 months. In the past 2 years, he had experienced pneumonia and empyema and, 7 months before admission to the clinic, he had "flu" and diarrhea for 2 weeks. Four months previously, he had pneumonia from which he recovered in 2 or 3 weeks, but shortly thereafter chills and fever occurred and had persisted. Examination revealed marked emaciation and pallor. There was a harsh systolic murmur over the base of the heart. The spleen was markedly enlarged. The concentration of hemoglobin was 4.5 gm. per 100 cc. of blood. The erythrocytes numbered 2,000,000 and the leukocytes 1200 per c.mm. The percentages of various types of leukocytes were as follows: lymphocytes 58, monocytes 2.5, and neutrophils 39.5. There were few signs of toxicity in the neutrophils, no immaturity, and good regeneration of erythrocytes. Repeated studies of the blood showed reticulo-endothelial cells on one occasion. The monocytes varied from 2 to 30%, and the total number of leukocytes from 1200 to 7400 per c.mm. Repeated blood cultures were negative, as were agglutination tests for typhoid, paratyphoid, Brucella, and tularense. Examinations of the sputum revealed no acid-fast bacilli. During his course in the hospital the patient's temperature ranged from 101 to 104° F. (38.3 to 40° C.), with a corresponding variation in the pulse rate. Blood transfusions and sulphanilamide were given. Five days before death, severe jaundice began and progressed in degree. Death occurred on the 19th day after admission to the hospital.

Necropsy. The spleen was found to be markedly enlarged, the weight being 1700 gm. There was focal necrosis in the spleen, liver, and lymph nodes of the mediastinum and abdomen. There was effusion of fluid into all the serous cavities. The thoracic duct was slightly dilated, but the cisterna chyli was markedly enlarged, bluish-red in color, and was filled with material of liquid consistency. The diameter of the cisterna chyli was 1.5 cm. and the trunks emptying into it were dilated to approximately four times their normal size. The duct, cisterna, and large branches were ligated and removed. Histologic sections revealed the cisterna filled by a large thrombus of fibrin, erythrocytes, and lymphocytes. The trunks were also filled with blood. The walls were thinned but no abnormality, such as leukocytic or lymphocytic infiltration, was seen. The adjacent lymph nodes revealed Hodgkin's disease (Fig. 4).

In this case, as in Case 9, there was thrombosis of blood in channels which normally carry lymph. There was no retroperitoneal hemorrhage to account for effusion of blood into lymph spaces and channels and no satisfactory explanation is forthcoming to account for it. Enlargement of the liver, spleen, lymph nodes, or any mass in the abdomen which compresses the venous channels could raise venous pressure locally and give rise to a reflux of blood into lymphatics through fortuitous lymphaticovenous communications.

CASE 11. The patient was a white man, aged 61. The chief complaints were loss of weight during the past 4 months, recurring epigastric distress relieved by alkali and food for the past 3 years, pain in the epigastrium

referred into the back, and vomiting of digested blood for the past 3 weeks. Examination at the clinic revealed marked emaciation and weakness. Roentgenologic examination of the stomach disclosed ulcerating carcinoma of the middle third. On gastric analysis, free hydrochloric acid was 36 and the total acidity was 76. The concentration of hemoglobin was 5.04 gm. per 100 cc. of blood and the erythrocytes numbered 2,000,000. At surgical exploration, partial gastrectomy for carcinoma of the middle third of the stomach was carried out. A posterior Polya type of anastomosis was made. Partial resection of the transverse mesocolon was necessary because of extension of the neoplastic process. On the 1st postoperative day the patient suddenly went into shock and died before supportive measures could be attempted.

Necropsy. Necropsy revealed hypertrophy of the heart with dilatation of the left ventricle. No residual carcinoma was found. The thoracic duct and cisterna chyli were grossly negative, but histologic examination of stained sections revealed a recent, trabeculated thrombus containing fibrin, erythrocytes, and lymphocytes occupying the lumen of the cisterna chyli.

In this case, shock with a rise of venous pressure occurred before death. There was a recent thrombus in the cisterna chyli. It is probable that a reflux of blood through lymphaticovenous communications along the course of the thoracic duct resulted in the appearance of blood in the cisterna chyli. Injury to the cisterna in the course of a surgical operation is not a likely possibility, as it is protected well by the muscles of the diaphragm where they originate over the lumbar vertebræ. However, trauma to lymph nodes in the mesentery and periaortic region may give rise to hemorrhage, and blood may appear in the lymphatic trunks which empty into the cisterna. In this case, either the first or third explanation offered is possible to account for blood in the cisterna chyli.

Case 12. The patient was a white man, aged 61. The chief complaints were a cough with production of much sputum for the past 4 years, fetid breath for 4 years, and marked loss of weight. In 1932, the patient had "flu" followed by thoracic pain, cough, and purulent sputum. A diagnosis was made, elsewhere, of pulmonary abscess. Three years before, he had experienced a pulmonary infection followed by hemoptysis and an increase in the amount of sputum. Phrenicectomy was carried out elsewhere. For the past 3 years there had been persistent, copious production of sputum and frequent hemoptysis. Loss of 52 pounds occurred during the past 4 years. Examination at the clinic revealed emaciation and fetid breath. There was transient auricular fibrillation, the fingers and toes were clubbed, and roentgenoscopic examination of the thorax revealed old fibroid lesions of the left apex and almost complete obliteration of the remainder of the lung by multiple large cavities. Bronchoscopy disclosed a deformity of the left main bronchus and purulent material filling the bronchus. A biopsy of the wall of the bronchus gave evidence of inflammatory material. The subsequent course was steadily downhill with fever and marked prostration. He died 7 days after bronchoscopic examination.

Necropsy. Necropsy revealed bronchiectasis with multiple abscesses in the left lung. There was hemorrhage into the bronchial cavities and organized pneumonia in the right lower lobe. The gall bladder contained multiple calculi and the wall was chronically inflamed. The thoracic duct above the diaphragm was surrounded by inflammatory tissue. Histologic examination of sections of the duct taken from this region showed lymphocytic infiltration of the periductal tissue and organization of inflammatory

tissue in the region. The muscularis of the wall of the duct did not stain well and the lymphatic vessels of the periductal tissue were filled with leukocytes and red blood cells.

In this case there was perilymphangitis of the thoracic duct. The wall of the duct was affected and, had the process been more acute, suppuration and necrosis might have taken place. No evidence of tuberculosis was found in this patient.

Summary. The thoracic duct has been examined in 119 consecutive autopsies. In this group, 8 cases were encountered in which the thoracic duct was involved in disease processes, namely, 1 case of suppuration, 1 of perilymphangitis, 4 of carcinomatous involvement, and 2 of thrombosis. In addition, 2 cases of suppuration and 2 of carcinomatous involvement were reported from necropsies performed previous to this study. In the series of 119 cases there were 43 different conditions found to be the primary cause of death. In none of 19 cases of peritonitis were there signs of inflammation or suppuration in the thoracic duct. Of 50 cases of carcinoma in this series 4 were associated with carcinomatous involvement of the thoracic duct.

In this small series, carcinoma and suppurative conditions were found to be the commonest conditions affecting the thoracic duct. There were only 2 cases of tuberculosis encountered in the series and neither of these gave evidence of involvement of the thoracic duct. It has been usually found that tuberculosis ranks second to carcinoma; the difference is probably due to the special type of cases met in this clinic.

Suppuration in the thoracic duct is rare and it is significant that, in the 3 cases reported in this study, all were secondary to suppuration in the periaortic lymph nodes. The presence of blood in the thoracic duct was encountered in many more cases than the 3 presented in the case reports. It is not uncommon to find blood in the sinuses of lymph nodes. Anatomically, it is easy to conceive of its passing from the lymph sinuses to the large trunks emptying into the cisterna chyli and thoracic duct. However, from the physiologic standpoint, this process would require a considerably higher venous pressure than usually obtains. It may be that this is an agonal process occurring shortly before death in the majority of cases. In the cases of thrombosis reported, the clots were well formed and, in one, the cisterna was greatly dilated, indicating that blood had been present for a longer period than could be accounted for by an agonal process.

The relation of the thoracic duct to the pathogenesis of disease conditions in the body has been considered in the comments given after the case reports. Were the cisterna chyli and thoracic duct examined routinely at necropsy in large series of cases, interesting conclusions might be drawn as to the spread of disease from one part of the body to another through channels other than those carrying blood.

BOOK REVIEWS AND NOTICES.

HANDBOOK ON SOCIAL HYGIENE. Edited by W. BAYARD LONG, M.D., Attending Dermatologist and Director of Dermatology and Syphilis Clinics in St. Luke's Hospital, New York, etc., and JACOB A. GOLDBERG, M.A., PH.D., F.A.P.H.A., Secretary, Social Hygiene Committee, New York Tuberculosis and Health Association, and Social Hygiene Council of Greater New York. With a Foreword by EDWARD L. KEYES, M.D., Professor Emeritus of Clinical Surgery (Urology) in Cornell University Medical College, New York. Pp. 442; 62 illustrations. Philadelphia: Lea & Febiger, 1938. Price, $4.00.

THE editors and 17 contributors have made a valiant effort to supply medical and interested lay people with a handbook on social hygiene. When one realizes the diversified audience aimed at, this book can be looked upon as more than a pioneering effort. It is truly a handbook covering every phase of the subject. Nowhere else, to the Reviewer's knowledge, is available an authoritative up-to-date compilation in so brief a compass of the data on social hygiene such as is here produced. Furthermore, in spite of the many contributors, a uniform style of presentation and unanimity of opinion on controversial subjects has been attained. Clarity and full understanding of the subject matter is assured for the casual reader by excellent concise summaries at the end of most chapters; the more enquiring reader is supplied with a rather complete bibliography at the end of each chapter. Thus, in a small book of some 400 pages, the editors have produced a compendium which is both informative and provocative of further study in the important and ever-dynamic subject of social hygiene.

With no desire to find fault, certain criticisms regarding important omissions or non-conventional points of view expressed in this work must be pointed out. Outstanding among the omissions are: summary of the facts of infectiousness, especially of syphilis; discussion of relapse or recurrence in syphilis; a specific week-by-week schedule, such as that of the Coöperative Clinical Group, for the treatment of early syphilis; and syphilophobia. It is a little distressing to a modern syphilologist still to have toilet seat infections or abortive cure of syphilis, mentioned without a condemnatory note. Syphilis is conceded to be systemic from the start, yet on page 43 one reads about secondary syphilis: "The eruption signifies that the spirochetes have gained entrance to the blood stream and have been carried to all tissues and organs of the body." Latent syphilis seems to be regarded as to some extent synonymous with late syphilis, since, after a careful statement of the necessity for complete study of a latent syphilitic patient before treatment is instituted, one of the collaborators goes on to discuss how treatment should be modified if cardiovascular or kidney complications are discovered in latent syphilitics.

While the first visit to a clinic is rated so important in case holding that "the majority of patients require no additional follow-up work," no detailed account is given anywhere in this book of the content of the first interview with the patient. Furthermore, follow-up by mail which is advocated in this handbook, does not in our experience compare at all favorably with personal follow-up methods.

If one ignores such occasional deviations or omissions, this work deserves the attention of physicians, nurses and social workers. It should not, however, be used by physicians as a substitute for more extended works on syphilis and gonorrhea. H. B.

CUTANEOUS CANCER AND PRE-CANCER. A Practical Monograph. By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Syphilology and Director of Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University; and ANTHONY C. CIPOLLARO, M.D., Associate in Dermatology, Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University. With a Foreword by FRANCIS CARTER WOOD, M.D. Pp. 222; 231 illustrations. New York: The American Journal of Cancer, 1937. Price, $3.75.

THIS practical little volume discusses the symptomatology, diagnosis, etiology, pathology and treatment of cancer of the skin and the precancerous dermatosis. There are 231 excellent illustrations. The photomicrographs are exceedingly fine. There are four general sections and a good index. A wide variety of precancerous lesions are discussed as well as the carcinomas and sarcomas of the skin. The lymphoblastomas are briefly reviewed, although the authors acknowledge that "strictly speaking they do not belong in the group of carcinomas and sarcomas." Each section is followed by an adequate and well-selected bibliography. The monograph is not intended as a reference book, but as a manual of undisputed facts. This work will receive wide recognition from general practitioners and surgeons as well as from the author's colleagues in dermatology as it should.

I. R.

METHODS OF TISSUE CULTURE. By RAYMOND C. PARKER, PH.D., Associate in Experimental Surgery, The Rockefeller Institute for Medical Research, New York. With a Foreword by ALEXIS CARREL, M.D. Pp. 292; 109 illustrations. New York: Paul B. Hoeber, Inc., 1938. Price, $5.00.

THIS book gives the essential details of the basic techniques developed in Carrel's laboratory. Many new and highly original methods are described which have not before been published, *e. g.*, Colonel Lindbergh's method for separating serum from plasma; others are modifications of techniques described in former articles.

The author's discussion of the main techniques involved in tissue culture work is so detailed and clear that from his descriptions and illustrations a beginner could certainly obtain a fairly comprehensive knowledge of the subject. He weighs one method of culturing different types of tissue against another, points out possible sources of error, recommends workable solutions, and on the whole clarifies the most essential problems to be encountered.

The greater part of the manual concerns itself with technical details which are necessary for the success of the tissue culture technique.

The Carrel flask culture method is fully described and highly recommended for growing all types of tissue. This method affords a relatively stable system in which both the effect of the cells on the medium and the effect of the medium on the cells can be studied simultaneously. The pH of the medium can easily be adjusted by Carrel's technique of gas control. The author prefers the flask method since it is applicable to more types of experiments and various tissue than any other method.

Tissue culture work on tumors has revealed a wealth of information concerning the nature of the cells themselves, their malignancy, and how they differ from normal tissue. One of the most important problems which first confronted investigators was whether the tumor cells retained their malignancy *in vitro*. As a result of experiments performed by Rous, Lewis, Carrel, and others, it has been proven that the malignancy of tumor cells is not lost even after innumerable transplantations or many passages through animals. Just as normal cells retain certain specific functional

properties when cultivated *in vitro*, so tumor cells retain their malignancy which "is a permanent characteristic located in the cell itself."

Most of the experiments on the propagation of viruses using tissue culture techniques have been done very recently. In this book the author reviews the most important work which has been done and is still being done in this field. Among such experiments are those on the species specificity of viruses, the propagation of viruses with living tissues without loss of virulence, and the vaccination of animals with virus material which has been developed not in animals, but in conjunction with tissue fragments in culture.

In summary, the author has analyzed the most important phases of tissue culture techniques and has presented clearly the most recent procedure and developments in the field. B. L.

THORACIC SURGERY. A Revised and Abridged Edition of Sauerbruch's "Die Chirurgie der Brustorgane." By FERDINAND SAUERBRUCH, Professor of Surgery in the University of Berlin; and LAURENCE O'SHAUGHNESSY, F.R.C.S., Hunterian Professor in the Royal College of Surgeons of England; Consulting and Thoracic Surgeon to the British Legion Sanatorium, Preston Hall, and to the Nottinghamshire County Council, etc. Pp. 394; 215 illustrations and 15 colored plates. Baltimore: William Wood & Co., 1937. Price, $13.50.

THIS revised and abridged edition of Sauerbruch's "Die Chirurgie der Brustorgane," which was published in 1918, and again in 1921, 1924, 1928 and 1930, will be most welcome. O'Shaughnessy has, in his translation and abridgment, accomplished something for which surgeons in the English-speaking world will remain in his debt. It is a volume which can be read with profit not only by the thoracic surgeon, but by general surgeon, internist and tuberculosis specialist. There are 17 chapters, a bibliography and an author and subject index. Lesions of the chest wall are reviewed as well as lesions of the pleura, lungs, heart and pericardium, mediastinum, esophagus and diaphragm. There is a separate chapter on the "Surgical Treatment of Cardiac Ischemia." The paper, type, composition and illustrations are excellent. Although in many minor points there may be some disagreement in methods of treatment, or in special techniques, the volume offers the opinion of one of the peers in the field of thoracic surgery. As such it will be widely received. No one interested in the surgical problems of the thorax can afford to be without it. I. R.

THERAPIE DER TUBERKULOSE. VOLS. 1 and 2. Herausgegeben von PROF. DR. J. BERBERICH, Frankfurt, und Dozent DR. P. SPIRO, Davos. Pp. 845; illustrated, 1 colored plate. Leiden: A. W. Sijthoff's Uitgeversmaatschappij, N. V., 1937. Price, Paper, Hfl. 25.00; Bound, Hfl. 28.50.

IN this work methods of therapy are based on present-day knowledge of the pathology, bacteriology, immunology and pathogenesis of tuberculosis. Authors are a distinguished group of investigators and clinicians predominantly continental, but including several workers now in England and America.

The first volume opens with a historical review of therapeutic concepts since Laennec. There follow chapters giving detailed consideration to bacteriologic and immunologic methods and theories. The chapters on the pathology of tuberculosis emphasize the changes that occur in response to various therapeutic measures. The diagnostic uses of tuberculin and Roentgen ray are concisely discussed. The volume is concluded by chap-

ters on tuberculin therapy, vaccination, chemotherapy, and occupational therapy.

In the second volume treatment is described system by system, including the upper respiratory tract, lungs, circulatory system, gastro-intestinal tract, reticulo-endothelial system, bones and joints, genito-urinary tract, skin, eye, ear and nervous system. In the chapters on pulmonary tuberculosis, rest treatment, the rôle of diet, climate and physiotherapy are discussed as well as symptomatic management. Collapse therapy and surgical procedures are more elaborately considered. Also of particular interest to the surgeon is the section on bone and joint tuberculosis, which includes admirably concise but detailed descriptions of operative methods. Chapters are devoted to the treatment of tuberculosis in children and in the aged, in diabetes and in the pregnant. Finally, there is a chapter on psychotherapy.

It is obvious that this work covers a wide field in considerable detail. There is some unavoidable repetition, but the inclusion of this wealth of material within two volumes is a tribute to the skill of the authors. There is an adequate index, and the contributors have in most instances appended extensive bibliographies. These volumes should be especially useful as a work of reference in any problem of treatment. H. H.

SYPHILIS, GONORRHEA AND THE PUBLIC HEALTH. By NELS A. NELSON, B.S., M.D., F.A.P.H.A., Director, Division of Genitoinfectious Diseases, The Massachusetts Department of Public Health; and GLADYS L. CRAIN, R.N., Epidemiologist, Division of Genitoinfectious Diseases, The Massachusetts Department of Public Health. Pp. 359; illustrated. New York: The Macmillan Company, 1938. Price, $3.00.

THE authors have endeavored to bring together, in condensed form and under one cover, the much diversified knowledge pertaining to the public health aspects of genito-infectious disease control. The work should be read not only by physicians interested in the rapidly developing national public health movement to stop the spread of syphilis and gonorrhea, but also by health officers and public health workers in general, and it might well form a text for nursing and social work courses in this field.

The first half of the book is devoted to a rapid and, from the standpoint of the physician therefore, a rather superficial review of the minimum essential medical knowledge. This section is authoritative and accurate for the most part, however, in that it follows precisely the standards developed in the study conducted by the Coöperative Clinical Group and the United States Public Health Service, and in that it often quotes from the works of the currently recognized medical specialists in these fields. The chapters devoted to the communicability of syphilis and gonorrhea are commended especially to those physicians dealing with the genito-infectious disease problem in the schools and in industry, and to all persons interested in the formulation of venereal disease control laws. As the authors point out, it is regrettable that the increasingly frequent practice of employers requiring their employees to have blood tests made and then summarily dismissing those who have positive tests regardless of the age of the infection or the amount of treatment given, is supported in many cases by physicians who should know better. And again, when dealing with the problem of communicability, "It is less embarrassing to accuse a toilet seat than to seek for sexual sources, or to request the examination of other members of the family." It requires so much less tact and no labor.

The general public health problem in the management of genito-infectious diseases, though clearly defined, have thus far evoked no generally effective

standard procedures or solutions, as have the purely medical aspects of the problem. In presenting this portion of the field the authors have accordingly seen fit in many instances to express a personal viewpoint which results from their local experience and which, therefore, may not have the advantage of widespread applicability *in toto* at least. It should not be lost sight of, however, that the authors have had as many years of active experience with these problems as have had most health authorities in this country, and that their accomplishments in Massachusetts have brought national recognition. N. I., JR.

NEW BOOKS.

The Medical Clinics of North America. Vol. 22, No. 4 (Mayo Clinic Number, July, 1938). Pp. 360; illustrated. Philadelphia: W. B. Saunders Company, 1938.

The 9 articles of the Symposium on Medical Emergencies will have many absorbed readers. Among the 35 authors is a larger number than usual of well known names.

The Vitamins and Their Clinical Applications. A Brief Manual. By PROF. DR. W. STEPP, Director of the 1. Medical Clinic, University of Munich; DOZ. DR. KÜHNAU, Director of the Municipal Institute for Balneology and Metabolism, Wiesbaden, and DR. H. SCHROEDER, Associate at the 1. Medical Clinic, University of Munich. Translated by HERMAN A. H. BOWMAN, M.D., Minneapolis, Minn. Pp. 173, with separate Index of 28 pages. Milwaukee: The Vitamin Products Company, 1938. Price, $4.50.

The Rheumatic Diseases. A Course of Lectures Arranged by the Medical Staff of the St. John Clinic and Institute of Physical Medicine. Edited by SIR LEONARD HILL, M.B., LL.D., F.R.S., Director of Research, St. John Clinic and Institute of Physical Medicine and Consultant to the Rheumatic Unit at St. Stephen's Hospital (London County Council), and PHILIP ELLMAN, M.D., M.R.C.P., Physician to St. John Clinic and Institute of Physical Medicine and Consultant Physician to the Rheumatic Unit at St. Stephen's Hospital (London County Council). With a Foreword by SIR ARTHUR MACNALTY, K.C.B., M.D., F.R.C.P., Chief Medical Officer to the Ministry of Health. Pp. 270; 46 illustrations. Baltimore: William Wood & Co., 1938. Price, $4.00.

Outline of Roentgen Diagnosis. An Orientation in the Basic Principles of Diagnosis by the Roentgen Method. By LEO G. RIGLER, B.S., M.B., M.D., Professor of Radiology, University of Minnesota, Minneapolis. Atlas Edition. Pp. 212; 254 illustrations shown in 227 figures presented in drawings and reproductions of roentgenograms. (Figs. 6 to 51 and 55 to 72 are drawings in an original technic by JEAN E. HIRSCH.) Price, $6.50. (Also Exclusive Text Edition from which the Atlas of Roentgenology has been omitted, but to which all figure references have been retained in the text. Price, $3.00.) Philadelphia: J. B. Lippincott Company, 1938.

Pathological Technique. A Practical Manual for Workers in Pathological Histology Including Directions for the Performance of Autopsies and for Microphotography. By FRANK BURR MALLORY, A.M., M.D., S.D., Consulting Pathologist to the Boston City Hospital, Boston, Mass. Pp. 434; 14 illustrations. Philadelphia: W. B. Saunders Company, 1938. Price, $4.50.

The Troubled Mind. A Study of Nervous and Mental Illnesses. By C. A. BLUEMEL, M.A., M.D., F.A.C.P., M.R.C.S. (ENG.). Pp. 520. Baltimore: The Williams & Wilkins Company, 1938. Price, $3.50.

A General Textbook of Nursing. A Comprehensive Guide to the Final State Examinations. By EVELYN C. PEARCE, Sister Tutor, The Middlesex Hospital, etc. Pp. 888; 176 illustrations. New York: E. P. Dutton & Co., 1938. Price, $3.75.

Cancer. With Special Reference to Cancer of the Breast. By R. J. BEHAN, M.D., DR. MED. (BERLIN), F.A.C.S., Cofounder and Formerly Director of the Cancer Department of the Pittsburgh Skin and Cancer Foundation, Pittsburgh, Pa. Pp. 844; 168 illustrations: The C. V. Mosby Company, 1938. Price, $10.00.

Life and Letters of Fielding H. Garrison. By SOLOMON R. KAGAN, M.D. With an Introduction by PROFESSOR JAMES J. WALSH. Pp. 287; 3 illustrations. Boston: The Medico-Historical Press, 1938. Price, $3.00.

The Horse and Buggy Doctor. By ARTHUR E. HERTZLER, M.D. Pp. 322; illustrated.. New York: Harper & Brothers, 1938. Price, $2.75.

Refraction of the Eye. By ALFRED COWAN, M.D., Associate Professor of Ophthalmology, Graduate School of Medicine, University of Pennsylvania; Attending Ophthalmologist, Philadelphia General Hospital, etc. Pp. 319; 172 illustrations and 3 colored plates. Philadelphia: Lea & Febiger, 1938. Price, $4.75.

Triumph Over Pain. By RENE FÜLÖP-MILLER. Translated by EDEN and CEDAR PAUL. Pp. 438; illustrated. Indianapolis: The Bobbs-Merrill Company, 1938. Price, $3.50.

Rheumatische Kreislaufschädigungen. By DR. SIEGFRIED DIETRICH, Dozent für innere Medicin, II. Medizinische Klinik der Charité, Berlin. Mit einem Geleitwort von PROF. DR. G. VON BERGMANN, Direktor der II. Medizin, Univ.-Klinik, Berlin. Band 7, Der Rheumatismus. Sammlung von Einzeldarstellungen aus dem Gesamtgebiet der Rheumaerkrankungen. Herausgegeben von PROFESSOR DR. RUDOLF JÜRGENS, Berlin. Pp. 204; 34 illustrations. Leipzig: Theodor Steinkopff, 1938. Price, Rm. 6.75.

Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung. XI. Tagung. Zu Bad Nauheim vom 26-27. Marz, 1938. Herausgegeben von PROFESSOR DR. EB. KOCH, Bad Nauheim. Pp. 430; illustrated. Leipzig: Theodor Steinkopff, 1938. Price, Rm. 11.25.

The History of Bacteriology. (University of London Heath Clark Lectures, 1936, delivered at The London School of Hygiene and Tropical Medicine.) By WILLIAM BULLOCH, M.D., F.R.S., Emeritus Professor of Bacteriology in the University of London. Pp. 422; illustrated. New York: Oxford University Press, 1938. Price, $3.75.

The British Encyclopædia of Medical Practice including Medicine, Surgery, Obstetrics, Gynæcology, and other Special Subjects. Under the General Editorship of SIR HUMPHRY ROLLESTON, BT. G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. *Vol. 8. Leukæmia to Mucous Colic.* With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GREY TURNER, D.CH., M.S., F.R.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. (ED.), F.C.O.G., SIR LEONARD ROGERS, K.C.S.L., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 712; 49 illustrations and 13 plates (5 in colors). London: Butterworth & Co. (Publishers), Ltd., 1938. Price, $12.00 per volume.

The more important of the 52 topics treated in this volume are Leukemia (by Janet Vaughan); several aspects of Liver Disease (by R. S. Aitken and others); and of Lung Diseases (by Maurice Davidson and others); Malaria (by Sir S. Rickard Christophers).

Experience in the *Management of Fractures and Dislocations* (Based on an Analysis of 4390 Cases). By the Staff of the Fracture Service, Massachusetts General Hospital, Boston, under the General Editorship of PHILIP D. WILSON, M.D., Surgeon-in-Chief, Hospital for Ruptured and Crippled, New York; Clinical Professor of Orthopedic Surgery, College of Physicians and Surgeons, Columbia University, etc. (23 Contributors). Pp. 1036; 1417 illustrations of which 1192 are line tracings of roentgenograms in case reports. Philadelphia: J. B. Lippincott Company, 1938. Price, $15.00.

Applied Anatomy. Functional and Topographical. By ROBERT H. MILLER, M.D., Associate Professor of Anatomy in the University of Tennessee, College of Medicine, Memphis, etc. Pp. 484; 55 illustrations and 16 colored plates. Philadelphia: Lea & Febiger, 1938. Price, $6.50.

Ueber die Beziehungen der Qualität des Nahrungseiweisses zum Ablauf des Betriebsstoffwechsels. By ADOLF BICKEL, Professor der Pathologischen Physiologie an der Friedrich-Wilhelms-Universität in Berlin. Heft 3, Schriftenreihe zur Schweizerischen Medizinischen Wochenschrift. Pp. 100. Basel: Benno Schwabe & Co., 1938. Price, Fr. 10.

The Healing Knife. A Surgeon's Destiny. By GEORGE SAVA. Pp. 310. New York: Harcourt, Brace & Co., 1938. Price, $2.50.

NEW EDITIONS.

Internal Medicine. Its Theory and Practice in Contributions by American Authors. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P., Professor of Medicine in the Tulane University of Louisiana School of Medicine; Senior Visiting Physician to the Charity Hospital, New Orleans. Pp. 1428; 35 illustrations. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $10.00.

Oreille Interne. Etude anatomo-pathologique et clinique Technique, histologique et experimentale. By CH. CLAOUÉ (de Paris). Pp. 227; illustrated. Second Edition. Paris: Editions N. Maloine, 1938.

A Textbook of Histology. Functional Significance of Cells and Intercellular Substances. By E. V. COWDRY, Professor of Cytology, in the School of Medicine, Washington University, St. Louis, Mo. Pp. 600; 323 illustrations, some in color. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $7.00.

A Textbook of Histology. By ALEXANDER A. MAXIMOW, Late Professor of Anatomy, University of Chicago, and WILLIAM BLOOM, Associate Professor of Anatomy, University of Chicago. Pp. 668; 542 illustrations, some in colors. Third Edition, completely revised. Philadelphia: W. B. Saunders Company, 1938. Price, $7.00.

Whereas the second edition of this book represented a complete recasting and condensation from the large first edition, this edition has been changed only to accommodate the advances of the past 4 years. The book continues to exhibit the various excellences and shortcomings of its predecessors.

A Textbook of Bacteriology. By THURMAN B. RICE, A.M., M.D., Professor of Bacteriology and Public Health at the Indiana University School of Medicine. Pp. 563; 121 illustrations. Second Edition, revised. Philadelphia: W. B. Saunders Company, 1938. Price, $5.00.

A few sentences from the Preface explain the nature of the work: "The text remains one for the student and practicing physician . . . the inclusion of a bibliography has been deliberately rejected . . . we have held the morphological and cultural descriptions of the various organs to the real essentials." While it is questionable whether this is the best method to pursue with good medical students, there is no denying the strength of its appeal, and its apparently successful result.

The American Illustrated Medical Dictionary. A Complete Dictionary of the Terms used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Nursing, Veterinary Science, Biology, Medical Biography, etc., with the Pronunciation, Derivation, and Definition. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., Lieut.-Colonel M.R.C., U. S. Army, etc. With the collaboration of E. C. L. MILLER, M.D., Medical College of Virginia. Pp. 1607; 942 illustrations, including 283 portraits. Eighteenth Edition, revised and enlarged. Philadelphia: W. B. Saunders Company, 1938. Price, $7.50.

In this edition over 3000 new words have been defined, so that the text of the volume has been increased by more than sixty pages. The Index to the numerous portraits and the Index to tables occurring through the text are desirable aids.

A Textbook of General Bacteriology. By EDWIN O. JORDAN, PH.D., Late Andrew McLeish Distinguished Service Professor of Bacteriology in the University of Chicago. Revised by WILLIAM BURROWS, PH.D., Assistant Professor of Bacteriology in the University of Chicago. Pp. 808; 197 illustrations. Twelfth Edition, revised. Price, $6.00.

"The section on oxygen supply and respiration has been entirely rewritten as have those on filtration and the isolation of bacteria in pure culture. A new figure has been added showing the types of bacterial filters commonly used. Perhaps the most extensive revision has been made in the chapter on virus diseases. . . . A section has been added on lymphocytic choriomeningitis and the sections on poliomyelitis and lymphogranuloma inguinale entirely rewritten. . . . Yellow fever has been amplified to include the newly discovered jungle fever. Numerous minor changes have been made such as a reconsideration of the bacteriology of diphtheria, the immunizing properties of typhoid vaccines, droplet infection and others."

Fractures of the Jaws. By ROBERT H. IVY, M.D., D.D.S., F.A.C.S., Professor of Maxillo-Facial Surgery, School of Medicine and Graduate School of Medicine, and of Clinical Maxillo-Facial Surgery, School of Dentistry, University of Pennsylvania, etc., and LAWRENCE CURTIS, A.B., M.D., D.D.S., F.A.C.S., Assistant Professor of Maxillo-Facial Surgery, Graduate School of Medicine, and School of Dentistry, University of Pennsylvania, etc. Pp. 192; 199 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $4.50.

The Principles and Practice of Medicine. Designed for the Use of Practitioners and Students of Medicine. Originally written by The Late SIR WILLIAM OSLER, BART, M.D., F.R.C.P., F.R.S., Formerly Regius Professor of Medicine, Oxford University; Professor of Medicine, Johns Hopkins University, Baltimore, etc. Revised by HENRY A. CHRISTIAN, M.D., LL.D., S.D., F.R.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard University; Physician in Chief, Peter Bent Brigham Hospital, Boston. (The 9th, 10th, 11th and 12th editions were revised by THOMAS MCCRAE, M.D., F.R.C.P., Formerly Professor of Medicine, Jefferson Medical College, Philadelphia.) Pp. 1424; illustrated. Thirteenth Edition. New York: D. Appleton-Century Company, Inc., 1938. Price, $9.00.

The Pathology of Diabetes Mellitus. By SHIELDS WARREN, M.D., Pathologist to the New England Deaconess, The New England Baptist, The Huntington Memorial, and the Pondville State Hospitals; Director of Massachusetts State Tumor Diagnosis Service; Assistant Professor of Pathology in the Harvard Medical School, Boston. With a Foreword by ELLIOTT P. JOSLIN, M.D. Pp. 246; 86 illustrations and 3 colored plates. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $4.75.

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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IRRADIATION IN CERVICAL CANCER.

Radiotherapy. Five years have elapsed since we have reviewed the subject of cancer of the cervix and it seems that an opportune time has arrived for skimming over the enormous literature that has appeared since that time in order to take stock of the situation as it exists at present. A casual survey of the world literature clearly shows that irradiation is supplanting the radical operation, although in some clinics, mostly foreign, surgical procedures are still employed in some cases.

The material from the irradiation clinic of Doederlein in Munich has been analyzed by Voltz[21] and presented in a concise form. In the years 1927 and 1928 there were 336 cases of cervical cancer seen of which 20 (5.9%) were not treated because they were absolutely hopeless and died within a few weeks. Of the 336 patients, there were 76 (22.6%) who were well 5 years later, or, excluding the 20 patients who were not treated, the rate of cure was 24%. Dividing the entire series into groups, it is seen that 44 cases in Group 1 showed 26 remaining well; of 88 in Group 2, there were 28 remaining well; of 125 in Group 3, there were 22 remaining well, while there were no favorable results in 79 cases in Group 4. For the period from 1913 to 1928 including the preceding series, there were 2202 cases of cervical cancer admitted of which 163 (7.3%) were untreated. Of this series, 395 (17.9%) were well longer than 5 years after treatment, which equals 19.4% of the patients treated. By groups, the favorable results were 167 of 370 in Group 1; 118 of 489 in Group 2; 103 of 797 in Group 3; and 7 of 383 in Group 4. These figures show relative cures of 45.1% in Group 1; 24.1% in Group 2; and 12.9% in Group 3. Taking Groups 1 and 2 together as representing the operable and borderline cases, there was a relative cure of 33.1%.

From Buenos Aires comes a report by Ahumada, Prestini and del Togno[1] based on their experience over an 8-year period with 607 patients treated with radium in four different ways, depending upon the type of involvement. They used intrauterine applicators and colpostats where possible, but if the cervical canal had become obliterated, radium needles were inserted into the cervix until a canal could be formed. The primary mortality was 0.3% or 2 cases, 1 from severe hemorrhage and 1 from an accidental injury to the bladder. The cases were closely followed after treatment and showed an absolute cure rate of 28.53%. The relative cure rate after a 5-year interval was 94.1% for Group 1, 40.8% for Group 2, or a combined rate of 46.3% for Groups 1 and 2. In Group 3 the rate of cure was 18.9% while there were no cures in Group 4.

Of 662 private cases of cancer of the female genitalia treated by Schmitz,[16] 80% were located in the cervix. He believes that the extent of the growth of cancer of the cervix is directly related to the curability rate. The time elapsed from the occurrence of the first symptom to the beginning of adequate irradiation apparently does not influence the end-results. The freely movable, clearly localized growth shows from 80 to 90% good results after 5 years. Such growths can only be discovered by routine periodic health examinations. Cancer of the cervix is probably always preceded by a low grade of chronic inflammation. The discovery of chronic cervicitis by follow-up examinations after infections, abortions and labors and its adequate treatment will prevent carcinoma later on. If a silent early carcinoma be found during such examinations and adequately treated at this time, permanent healing may be achieved in nearly every case. In his series of 398 cases there are 90 (22.67%) of 5-year good end-results. Classified according to groups, the analysis shows that in Group 1 there were 36 cases with 31 (87.87%) cures; Group 2 included 53 cases with 25 (47.17%) cures; Group 3 contained 180 cases with 33 (17.78%) cures; while Group 4 contained 129 cases with only 1 (0.78%) cure.

At the Mayo Clinic, according to Bowing and Fricke,[4] the treatment with radium is by the intensive, broken-dose method, employing in most cases the universal silver tube containing 50 mg. of radium sulphate or 50 mc. of radon. Most patients receive supplemental Roentgen irradiation following the course of radium therapy. In their series of 1491 cases, extending over a period of 15 years, although the great majority of patients (91%) were in an advanced stage of the disease, of the entire number 26.8% lived 5 or more years without evidence of recurrence. The curability by groups was 69.2% for Group 1 and 60.2% for Group 2. That there is little risk to the treatment is shown by the fact that the hospital death rate for the entire series was only 1% and was confined to the group with advanced lesions.

Schreiner and Wehr[17] present a series of 937 cases treated by irradiation at the State Institute for the Study of Malignant Diseases, Buffalo. Their 5-year rate of relative curability was 64.8% for Group 1; 32.7% for Group 2; and 18.28% for Group 3. It can be seen from their report that cancer of the cervix occurs in every period in adult life, the youngest patient being 20 and the oldest being 83, and that there is a gradual increase in the percentages in each 5-year period up to the maximum of 55, and then a decline. They state that not much can be learned

of the extent of the disease from the symptoms as the disease may have been present from a few weeks to several years with almost identical symptoms. A study of the nationality of the patients was of no importance except that there was only one Jewess among 955 patients.

The experience and routine at the Memorial Hospital, New York, have been frequently presented by Healy,[10] who states that in most clinics except his, treatment with radium precedes treatment with Roentgen ray, if the latter is used at all. In a critical review of their cases they were impressed by the high percentage of extensively ulcerated and infected cases coming for treatment in which the adjoining normal tissues were considerably involved in reactionary changes. It seemed highly desirable to them to spend a short time in an effort to prepare the lesion for the application of radium. A great part of the surface growth of these advanced cancers consists of an infected tissue which is very easily destroyed under Roentgen ray therapy alone. Therefore they felt that they might obtain greater regression and a higher percentage of cures with fewer complications if all patients with ulcerated cancers of the cervix were first given high voltage Roentgen ray treatment, together with frequent vaginal antiseptic douches for a period of about 10 days preceding the application of radium. However, in all favorable cases radium is used first, as in such cases there is practically no infection and the lesion is small, the Roentgen ray cycle is then given as promptly as seems feasible after the radium. They believe it advisable to give a second Roentgen ray cycle 8 to 12 weeks after the first series has been finished.

It should be emphasized that external radiation is not used with the idea that it will cause glandular metastases in the deeper portion of the pelvis to disappear since the amount of radiation which reaches the deeper structures is not sufficient to have much effect, but rather it is used because it brings about changes in the connective tissue which help to interfere with the growth and activity of the cancer cell as well as with their lymphatic spread. More specifically, the plan of treatment at the Memorial Hospital consists of: (*a*) a high voltage Roentgen ray cycle of 4 treatments of 700 R units each; (*b*) 10 to 14 days later, radium is applied to the vaginal surface of the lesion by means of vaginal applicators for 1000 to 2000 mc. hours; (*c*) the following day under anesthesia 2 radium capsules in tandem formation are placed in the cervical and supracervical canals for 2000 and 1000 mc. hours respectively; (*d*) 8 weeks following the first Roentgen ray cycle a second similar Roentgen ray cycle is given. During the treatment and until the cervical lesion is entirely healed the patient is advised to use vaginal douches of potassium permanganate once or twice daily. Interstitial radiation with needles or seeds is not used as a routine but may be used as a later treatment for any portion of the lesion that fails to regress. With the routine use of Roentgen ray first, the appearance of the primary cervical lesion changes markedly, the superficial infected fungating surface disappears, the surrounding edema subsides, the lesion is smaller and the uterus acquires more mobility. The lesion and adjoining tissues are then in much better condition to respond satisfactorily to radium applications and there seems to be less constitutional and pelvic disturbance following radium treatment. While Healy considers irradiation the treatment of choice in most cases of cancer of the

cervix, occasionally surgical treatment is advisable in cases of pyometra which do not respond to drainage and in radiation-resistant cases which seem to increase in extent following irradiation. If pyometra is present when the patient is first seen, a rubber catheter is placed in the uterine cavity for drainage and to permit daily cleansing of the uterine cavity with weak antiseptic solutions, and in the meantime deep Roentgen ray therapy is carried out. If the pyometra subsides, radium is applied in full or divided doses. When pyometra develops as a late or post-radiation lesion, it is best treated by hysterectomy.

Ward and Sackett[23] outline the standard technique which is employed at the Woman's Hospital, New York. In cachectic cases the patient's resistance is improved by preliminary blood transfusions; a small dose of spinal anesthesia is used instead of a general anesthetic if there is no contraindication. They use an initial dose of radium of from 3600 to 4200 mg. hours, depending upon the extent and size of the growth, but in exceptional cases of extensive disease they have used over 6000 mg. hours as the initial dose. As a rule, 100 mg. is placed in the cervical canal and several 12.5-mg. needles are inserted at the junction of the cervix with the vaginal fornix. They stress the importance of distance screening by distending the vagina with gauze to its capacity to keep the bladder and rectum as far away as possible from the radium rays, and they use a self-retaining catheter to keep the bladder collapsed during the radium application. The outstanding feature of their method is the frequent follow-up inspection made by the surgeon himself throughout the 5-year period. During the first 3 years a monthly inspection is made and after that the patient is seen every 2 or 3 months. If the follow-up examination shows a beginning recurrence a further irradiation is given to check it in its incipiency. These late irradiations are of small dosage, averaging from 300 to 1200 mg. hours, usually in the form of platinum needles. The results of their 18 years' experience with radium show a 5-year salvage of 27.4% of 595 patients seen and 28.5% of the patients treated. In the cases of early cancer in which the disease was limited to the cervix they saved 56.2%. Of 359 patients seen over a period of 10 years the absolute cure rate was 17.3% and the relative rate was 18%. In spite of lowered life expectancy, 73% of those who survived 5 years lived 10 years or longer. They believe that the extent of the disease is of greater importance than the type of cell in determining the probability of cure, since they found early carcinoma had twice the curability of late carcinoma, irrespective of the maturity of the cells and of whether they were of the squamous or adenocarcinomatous type.

A marked improvement in results has been obtained by Pitts and Waterman[14] since they have changed their technique of application of radium from the simple intrauterine radium capsule to the use of parametrial irradiation by means of multiple needles. They found that they could implant long needles in the parametria and out into the broad ligament and in the vesicovaginal and rectovaginal septum without any difficulties or untoward results. They also found that there was not so much slough and that the cervix returned to normal appearance sooner under this treatment. Their plan consists of placing four 3-mg. needles out into the tissues at the sides of the uterus, 2 needles on each side. They then thrust a series of 2-mg. needles at 1- to 2-cm.

intervals in front and in back of the cervix, using in all from 12 to 16 needles. In the cervical canal they place a 20-mg. platinum capsule, holding it in place with a strand of silkworm gut, or in many cases they still use a tandem of two 50-mg. tubes. They have gradually increased the time of application until now they are allowing the radium to remain from 144 to 168 hours. While there has been a very satisfactory improvement in the results in all types treated, it has been most marked in the cases belonging to Group 3, where the absolute survival rate has increased from 14% under the old method to 29% under the plan of interstitial irradiation. This rate of cure is very high for cancers in Group 3 and therefore their method deserves careful consideration from all who employ radium.

Based upon a study of the world literature from 1912 to 1928, Dietel[6] states that of 7814 women with *inoperable* cancer of the cervix who were irradiated, 881 (11.3%) remained healed for over 5 years. Subdividing this collected series he found that healing occurred in 9.9% of those who were treated with radium alone, in 10.5% of those only receiving Roentgen therapy and in 13.4% of those receiving combined radium and Roentgen ray treatment. It would appear, therefore, that the combined treatment offers the best results, and of the various methods of combined treatment, he believes that the technique of the Heidelberg Clinic surpasses the others. This method consists of an intensive Roentgen irradiation of the parametrial tissues after the application of a full dosage of radium, taking precautions to avoid injury to neighboring organs.

Operation Combined With Irradiation. Since 1919 at the Cancer Institute in Ghent, Belgium, Daels[5] has been experimenting with the problem of applying radium to the uterus after exteriorizing the pelvis by surgical operation. After making a low transverse abdominal incision, the lower edge of the peritoneum is sutured to the skin above the pubis and inguinal canals. The peritoneum of the posterior wall of the pelvic inlet is incised transversely to the mesosigmoid, the upper edge of the peritoneum sutured to the anterior parietal peritoneum, the lower edge sutured to the upper edge of the skin incision. In this manner a new pelvic diaphragm is made at the level of the sacral promontory which closes the peritoneal cavity from the pelvis, and the radium can be applied to the various parts of the pelvis under direct vision. The pelvic organs can be irradiated with an even distribution of the rays, there will be no injury to the connective tissues, a longer application and a stronger dose can be given and any infected secretion will have an easy outlet. If better exposure be desired the infundibulopelvic ligaments can be cut or an easy hysterectomy can be done because the clamps can be left in place. The implantation of radium is not done until from 3 to 5 days after the operation has been performed, packing off the bladder and rectum with gauze-covered lead plates, 1 to 2 mm. thick. In the first 20 cases treated by this method there was only 1 death and that was due to a severe infection. More recently, in order to irradiate the pelvic lymph nodes, he has been using curved metal tubes in which radium can be placed and spaced. The tubes are of different sizes and curved, so that they can be brought into apposition with almost any part of the pelvis. In introducing these tubes a short low midline incision is made and the fingers introduced for the purpose

of orientation. The curved tubes are then introduced through lateral abdominal stab wounds and placed by the sense of touch of the fingers within the abdomen. Usually 2 tubes are placed in each side of the abdomen.

In the plan advocated by Gellhorn[8] the abdomen is opened by a midline incision, the intestines packed away and the pelvic cavity is exposed to sight and touch. The operator inserts the index and middle fingers of his left hand beneath the sterile drapings into the vagina, and proceeds to do a bimanual examination with the other sterile hand inside the abdomen. It is astonishing how much one can learn by this sort of examination. The extension of the cancer is almost always found to be greater than was assumed before the operation. After this exploration, gold seeds containing radium emanation are inserted beneath the peritoneum in such a way that these seeds form a complete ring around the periphery of the cancerous area. The guiding fingers in the vagina not only help in selecting the places where the seeds are to be introduced but also make it possible to gauge the exact depth to which the needles have to be pushed. The operator then withdraws from the operating table while an assistant closes the abdomen. The patient is then placed in the lithotomy position and the operator inserts one or more capsules of radium into the uterine cavity and radium needles into the tumor itself, particularly its outer edge. The total irradiation amounts to between 4200 and 4500 mg. hours, over one-half of which is obtained from the gold seeds. The peritoneal reaction is no greater than after any laparotomy and the small gold seeds produced no local necrosis nor irritation as foreign bodies.

In the borderline cases of cancer of the cervix, Taussig[20] frequently combines irradiation with surgical removal of a large portion of the tributary lymph nodes. Careful selection of the cases must be made as the patient must be a good operative risk and should preferably be of the younger age group. Of his 46 patients, the average age was 41 years. His plan consists of giving 1000 to 1500 R units of deep Roentgen ray therapy spread over 2 weeks. Two weeks after this series is concluded iliac lymphadenectomy is done under spinal anesthesia. Two weeks after the operation an intrauterine application of 4000 to 5000 mg. hours of radium irradiation is given and this is followed by an additional 2000 to 2500 R units of deep Roentgen ray therapy. The difficulties of the operation are not great and thus far he has not injured the large vessels although the dissection approximates them closely.

Comparison of Operation With Irradiation. The opinion of Shaw,[19] of England, as to the relative value of operation and irradiation in the treatment of cancer of the cervix is of great interest because he has been identified with the first operations of the kind which were done in Manchester. Although the time consumed in performing the operation has gradually been reduced until now it is only an hour in favorable cases, he considers the operation the limit of human endurance. He believes that every operator has to acknowledge a mortality of 20% in his first 100 cases, though the rate steadily improves with experience. In his last 20 cases he had only 1 death and of his entire reported series of 154 cases there was an operative mortality of 21.4%, with

38.3% alive and well after 5 years. In comparison with these figures he has treated 94 cases with radium alone, with 41.4% alive and well after 5 years. It seems to him, therefore, that he is getting the same percentage of cure with radium as with the radical operation, but with this great difference, namely, that the radium cases include advanced as well as early ones, while the operation list includes only the early and borderline cases. Even if the results with radium were just as good and no better than those with operation, he feels that radium would be the treatment of choice. There is such a slight mortality and the convalescence is painless, whereas after Wertheim's operation a large percentage of the patients are very ill for some days, and at the best are very slow in their recovery. The value of these figures lies in the fact that they are from one clinic and are free from personal bias. Although Shaw is well qualified to perform the radical operation and has had much experience with it, he has come to the conclusion that radium offers the best chance of cure and is the more humane method of treatment.

In the gynecologic clinic at Kiel, according to Schroeder,[18] there were 604 cases of cervical cancer under treatment from October, 1922, to December, 1930. Of these, 50% were operated upon, 178 by the Wertheim operation and 124 by the Schauta method. The primary mortality of the Wertheim cases was 18% while the Schauta group had a 1.5% mortality. The curability rate was 36% for the Wertheim group and 51% for the Schauta group. There were 253 cases treated with radium, of which 51 were in an operable stage. Of the operable group, there were 42% cures, while of the 202 inoperable cases 10% were living at the end of 5 years and there was a primary mortality of 16.5%.

Another comparative series has been presented by Plate[15] from the gynecologic clinic at Amsterdam with results that also confirm that radium should supplant operation. Of 193 cases in this series treated by radium, 72 were well after 5 years, a curability rate of 37.3%, whereas of 70 patients subjected to the Wertheim operation, 22 (31.4%) were well at the end of 5 years.

Mortality Studies. From the Mayo Clinic comes a report by Fricke[7] based upon 1117 patients who were treated by radium and Roentgen rays. Of these, 13 died during the primary course of treatment, a primary mortality rate of 1.16%. Comparison of the findings at necropsy of patients who died during the first course of treatment and of those who died during subsequent visits disclosed that acute pelvic infection and hemolytic streptococcic septicemia accounted for most of the deaths in the first group. A rather unexpected finding was that there were as many patients with metastases to the lymph nodes in the first group as in the second, and that there was a greater number with distant metastasis in the first group than in the second. Distant metastases occurred mainly to the lungs and the liver, were unsuspected and by present clinical methods were undiscoverable. From this study he believes that the prognosis in every case accepted for treatment must be very guarded. The relatives must be instructed that distressing complications may occur and that these complications often terminate fatally, even though the patient appears to be in good general

health. The best method of keeping the mortality rate as low as possible is by thorough study of each case and with suspicion of metastatic involvement or of impaired renal function, to limit treatment so as not to place undue stress on the patient. Such patients should be treated for palliation and not for cure. The broken-dose method of treatment seems preferable to the massive-dose technique, the effect appears to be gentler and on the appearance of any serious complication, irradiation may be instantly abandoned.

The histories and necropsy records of 166 patients who died from cervical cancer in the Philadelphia General Hospital have been studied by Behney,[3] who found that only 7 (4%) died from causes which were not dependent upon the presence of cancer. In the older patients, death was caused by secondary infection twice as frequently as in the younger ones. In the latter group, death was more often the result of some mechanical cause such as obstruction of the ureters or hemorrhage. The more anaplastic the type of tumor, the more frequently did metastasis occur. Involvement of the pelvic sympathetic nerves was demonstrated and he suggests that this involvement may be a factor in the production of pain and perhaps the interruption of impulses through these nerves by invading tumor cells may be the explanation for the occasional spontaneous disappearance of pain in patients with advanced disease.

Morton[12] studied 36 autopsies upon women in whom cervical cancer had been treated by irradiation. It was found that cases which were advanced when first seen usually died because of the local extension and that metastases were frequently absent. Patients adequately treated lived longer and death was due more often to metastatic lesions, probably because the local growth was held in check while metastases had time to occur, or those already present had time to mature and kill the woman. In the inadequately irradiated patients, the local growth was usually responsible for death.

Histologic Studies. From their studies at the Memorial Hospital, New York, Arneson and Stewart[2] emphasize the necessity of increasing the dose of Roentgen rays to the parametrium if any marked improvement is to be made in the cure of cervical cancer. They studied the clinical and pathologic changes occurring following different amounts of external irradiation delivered to the primary tumors of the cervix, with the hope that they might prove an index of what was going on in the parametrial extensions. They found that the quantity of external irradiation introduced into the primary tumor by the methods so far employed will not cure more than a very small percentage of cervical cancers and therefore cure of parametrial disease is equally rare. Furthermore, it is unlikely that the usual dosage which is applied to the parametrium will lead to any marked restraint in growth in the average case. On the other hand, there is both clinical and histologic evidence of marked regression of the primary lesions, even if cure is not obtained. There is a very decided difference in the dosage which will produce marked regression clinically and that which will produce complete histologic sterilization. The question arises whether under such circumstances it is worth while to pursue a protracted course of external radiation. They believe that it is, not because it will result

in a decided increase in the curability of the average cervical cancer, but because it may be a factor of importance in an occasional case. There is a large gap between the 3.2 threshold erythema doses delivered by the present methods and the 6 to 8 threshold erythema doses which they found most effective in radium treatment of the average primary cervical cancer. It is possible to close this gap partially if one is willing to accept a greater degree of initial cutaneous reaction and rectal and vesical irritation as the dose delivered by external irradiation is increased. Although this may be unwarranted in favorable early cases, it seems well warranted in borderline and advanced clinical cases in which conservative methods have little to offer.

In discussing the relationship of histologic structure to radiosensitivity, Norris[13] states that this relationship is a complicated one owing to the fact that so many factors enter either directly or indirectly into the question. Among these may be mentioned the location of the tumor, its accessibility, the character of its bed, the distance, and the type of intervening tissues; whether the neoplasm is papillary or infiltrating; the character of its blood supply; whether the blood-vessels possess thick or thin walls, their situation, whether central or peripheral, the general vascularity of the new growth, the size and perhaps the shape of the neoplasm, the character of the tumor cells, the degree of maturity, the proportion of immature cells, the relative number of cells undergoing mitosis, the amount of adipose tissue present, the rapidity of growth of the tumor, the relative amount of fibrous tissue and the desmoplastic property of the neoplasm; whether or not there has been previous irradiation, the presence of infection, the general condition of the patient, her age, the presence of syphilis, tuberculosis or trauma caused by earlier operative procedure, the degree of anemia, cachexia, or ischemia, hereditary influence of the tissue from which the tumor had its origin, the presence of metastases and perhaps even the social status of the patient. Intensity of irradiation, dosage, distance, filter, duration of exposure and other factors also enter into the problem. It is apparent, therefore, that the entire subject of radiosensitivity of tumors is so complex and influenced by so many factors that positive conclusions regarding individual cases are difficult of attainment. It is generally conceded that the degree of anaplasia and the amount of mitosis are definite factors in producing radiosensitivity and yet it is well known that both may vary markedly in different sections of the same tumor. When considered in large groups he believes that a certain amount of dependence may be placed upon histologic grading, but when applied to individual cases this becomes extremely uncertain. In general, papillary tumors are more sensitive than are those of the infiltrating type. It is probable that the type of circulation is an important factor in determining radiosensitivity. Neoplasms that are soft, friable, highly vascular and of the papillary type usually undergo marked regression and disappear rapidly under suitable irradiation. Hard, infiltrating tumors within the cervical canal seem to be much more resistant.

Complications of Irradiation. Attention has been directed by Jones[11] to a new clinical entity that may develop and call for surgical intervention months or years after complete regression of the cervical cancer.

This condition is a benign stricture of the intestine that might easily be confused with metastatic carcinoma. The rate of recurrence of cancer is so high that almost any abdominal or pelvic pain may be attributed to malignant extension or metastasis. If the condition is actually a benign stricture caused by irradiation, it is quite obvious that additional Roentgen ray treatment would only aggravate the condition. Therefore, one should always keep in mind the possibility that a patient who exhibits unusual abdominal disorders, particularly if they simulate intestinal obstruction, several months or even years following radiation therapy, may have a stricture of the intestine and may be restored to normal health by resection of the lesion. Before this disability is attributed to metastasis, thorough reëxamination by sigmoidoscopic and roentgenographic studies should be made to eliminate the possibility of this curable complication. While Roentgen examinations demonstrate lesions in the sigmoid quite readily, strictures in the small intestine are quite difficult to visualize unless the obstruction is practically complete. In this type of case it is inadvisable to give barium in any large amount and therefore exploratory laparotomy is warranted, especially in patients in whom there is no evidence of recurring carcinoma in the pelvis. As to the cause of these strictures, Jones believes that the initial insult is delivered by radium. If a loop of small or large intestine remains in the same position in the cul de sac during the entire time of radium irradiation, the erythema produced at this point may be sufficient to produce a simple local peritonitis which would fix the bowel at this point temporarily, and before the exudate is completely absorbed, Roentgen rays are administered, thus furnishing additional irritation, which is sufficient to cause an ulceration in the mucosa that eventually goes on to stricture formation. As time passes, the exudate is absorbed and the bowel becomes free, which is the general finding at operation. To prevent this complication, a change of position of the patient during the treatment suggests itself as an aid, but this would not be entirely safe, for fear of dislodging the radium tubes and possibly causing damage to the rectum or bladder. However, a Trendelenburg position maintained during treatment may help to keep the intestine out of the pelvis while the latter is being irradiated both by radium and by Roentgen rays. If the theory of some fixation of a loop of intestine is tenable, drugs to stimulate peristalsis may be administered and he believes that it might be advisable to give from 0.5 to 1 cc. of pitressin every 4 hours while the radium is in place in order to keep the intestine moving, and thus to preclude excessive irradiation of any one loop.

Complications affecting the urinary organs are discussed by Graves, Kickham and Nathanson.[9] They state that there are two types of radiation reaction within the bladder. First, there may be the early or acute reaction which occurs at the height of the radiation effect in the cervix itself. This varies in degree, gives rise to symptoms of cystitis and either subsides or goes on to ulceration or even fistula formation. The late radiation reaction results from vascular changes which may vary in degree from mild transient interference to complete obliterative endarteritis with ischemic necrosis, and the lesion produced in the bladder will depend upon the extent of these effects. The symp-

toms consist of dysuria, hematuria and increased frequency, occurring long after the treatment of the cervix. Clinical differentiation between a late radiation reaction and invasion by tumor may be difficult and sometimes cannot be made by the cystoscopic picture alone. A history of radium treatment of the cervix followed by a prolonged interval of many months before the appearance of the bladder lesion favors the diagnosis of radiation reaction. In every instance of late radium reaction in their series, radium seeds, occasionally glass but usually gold, were used in the treatment of the cervix. They believe this to be of great significance, since inadequate filtration and the site of insertion in the periphery of the growth undoubtedly play the greatest part in the production of this complication. Obstruction of the ureters is another frequent complication, since they found it present in 70% of 257 cases of cervical cancer. Because of this they urge that complete urologic investigation be included in the management of this disease. In this way, measures of relief may be made available for the pain and distressing symptoms of uremia which so often confront these patients. Such measures of relief may be simple dilatation of the ureter by means of a catheter, nephrostomy, ureterostomy or nephrectomy, according to the severity of the case.

In the experience of Ward,[22] upper urinary tract disease was usually a late development and generally due to obstruction of the ureter, which could usually be demonstrated by catheter at about 4 cm. from the ureteral orifice. The action of radium which produces a proliferation of connective tissue with subsequent contraction is responsible for the complication in many cases, due to the proximity of the ureters to the sides of the cervix as they pass through the base of the broad ligaments, although the invasion of the carcinoma into the same region is a frequent cause. He urges that in the follow-up of these patients we should watch for urinary disturbances, as the early discovery of ureteral stricture may allow of its being relieved by simple dilatation, or if necessary a nephrectomy may be done.

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DERMATOLOGY AND SYPHILOLOGY.

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SYPHILIS IN INDUSTRY

A REVIEW OF PROBLEMS AND POLICY.

THE rapid development of the public health campaign against syphilis in this country has precipitated the disease upon the lap of industry with a suddenness probably as disconcerting to industry as to the victims of the infection. Inevitably every unforeseen or difficultly controllable contingency in the general campaign mirrors itself in varying grades of miniature in the problems and methods of the industries which have taken cognizance of the matter. The first consideration on which investigation and writing have been active for a quarter-century, is that of the industrial prevalence of the disease.

Prevalence of Syphilis in Industry. In offering the following series of estimates, account should be taken of the fact that they are based almost entirely upon the use of a single uncovering method; namely, blood serologic tests. They will inevitably, therefore, reflect the problems of false positiveness and false negativeness, and of artificial selection (as in the avoidance of industries known by syphilitic or non-syphilitic workers to require blood tests as conditional to employment). One of the earliest American studies of occupational distribution of syphilis was that of Stokes and Brehmer[25] at the Mayo Clinic (1920) in which the examination of 1143 Mayo Clinic patients, classified by occupation, disclosed 11.7% syphilis in railroad employees, 6.1% in laborers, 3.8% in merchants and tradesmen, and 1.5% in farmers. In 1921, Williams[28] reported 4.4% syphilis in apparently healthy applicants for work. The medical service of a manufacturing company,[22] in 1923–1925, reported among skilled, semi-skilled and clerical workers to the number of 3447, an incidence of 3.5% syphilis. The Endicott-Johnson shoe manufacturing interests,[14] in 1928, reported 3.7% syphilis in 4117 workers. The Seattle City Health Department[5] found in 1927–1931, among milk-handlers and drivers of public conveyances, 3.7% syphilitic among 26,408 persons. The City Health Department of San Francisco[5] in 1930, among 700 examinations, found 4% syphilis in milk-handlers. Barbers in Oklahoma,[5] in 1930, rated 13% syphilis. A West Virginia coal company,[5] in 1931, reported 8.5%

syphilis among 4448 employees, which included 5.1% among American whites, 16% among American negroes, and 6.4% among foreign-born employees. In Minnesota, the Employment Stabilization Research Institute[5] in 1931 reported, among unemployed casual laborers, 8.4% syphilis in 227 examinations. Parran[20c] quotes the following figures, based on collected data of the Office of Industrial Hygiene of the Public Health Service, and material obtained by members of the Association of Industrial Physicians and Surgeons, as reported in Detroit, May 19, 1936. Of 15 companies making routine blood tests in a total of 80 companies represented, 4.8% syphilis was found among 110,675 employees. Among 21,239 applicants for positions, only 2.3% were positive, which Parran believes indicative of the tendency on the part of industrial workers to avoid occupations where routine blood tests are to be expected. The Eastman Kodak figures[20a] among 4000 applicants are given as 1.1% syphilis. Nine railroads requiring tests on routine applications for jobs gave among 21,026 applicants, 7.8% syphilis.[20] Some of the railroads, possibly because of their geographic situation, reported considerable lower percentages (5%, 4.04%). The E. I. duPont de Nemours Company,[9] among 36,794 employees, reported 4.2% positive blood reactions for syphilis. The U. S. Coast Guard[21] shows an interesting differentiation between personnel in the sea service and the life-saving service; 5.7% in the former and 0.4% in the latter. Long,[13] from the medical service of the Gulf Refining Company, Port Arthur, Texas, reported 32% positives in 900 negroes, and 5 to 10% positives in 1400 tests on whites. The Caterpillar Tractor Company (Vonachen[27]) disclosed 4% syphilis in 9450 employees.

From this résumé, by no means complete, it is clear that the incidence and prevalence of syphilis varies markedly with occupation, with race, and with the geographic location of the industry. For instance, agricultural and industrial labor in the South runs high in syphilis (12 to 35%) according to the U. S. Public Health Service surveys.[12] It is therefore clear that any industry which draws from a population type such as the negro, in which the incidence of the disease is intrinsically high, will inevitably reflect its prevalence.

The Cost of Syphilis to Industry and Labor. Figures of this sort have still a somewhat speculative character. Many of them are old and possibly outdated; based on individual surveys of industries whose identities are concealed and whose representative character for the problem in general or the country at large cannot be determined. Among the most quoted estimates are those of Parker[19] (1932), including 12% syphilis in a group of railway employees exhibiting delayed convalescence and disability whose total loss of time represented 13,946 days, and $48,711. A large industrial concern, unnamed, whose personnel efficiency had dropped below expectations, found that 1 in 10 employees had gonorrhea or syphilis, 68% of the non-effective employees were on the sick list because of these diseases, and those venereally diseased had lost three times as much time as persons not affected. Each person with syphilis or gonorrhea was paying out an average of $75 a year for such treatment as was being given. The establishment of a clinic within the industry for adequate treatment and assistance to these persons presently offset the cost of the establishment by increased production. A West Virginia manufacturing

concern, as a result of the installation of a clinic for venereal disease costing $5000 to $6000 for the first year, sustained an increased efficiency of 35%.

It is clear from a review of the literature that statistics providing adequate differentiation among types of employees, types of industry, and obtained by methods other than mere routine serologic testing of blood, are really needed before the problem can be envisaged in its entirety, and principles formulated.

The Kind of Syphilis in Industry. It is a notable fact, one of the first items in the primer of modern syphilology, which is as yet so unfamiliar to many, that the kind of syphilis that a person has rather than the mere fact that he has syphilis, is of major importance. The effort to differentiate syphilis into its industrially and medically significant and insignificant phases has thus far made very little progress. To the syphilologist, the blood testing of employees is no more than the merest first step; competent medical examination of the candidate for employment or the employed person is the only means by which infectious syphilis will be differentiated from non-infectious, and syphilis which is industrially dangerous can be separated from syphilis which is a liability, but not a danger. The expectation, of course, must be that serologic uncovering methods will disclose an enormous amount of latent syphilis of which the victims are in general entirely unaware. Those writing on the subject have no difficulty in supplying harrowing case incidents of deserving employees discharged after years of useful service, merely upon the basis of a single positive blood test. The current possibilities of misapplication or unjust discriminations based on blanket legislation covering such groups as food-handlers is also obvious to any syphilologist. A worker in the laboratory of a milk-handling concern, though he never have contact with milk, can be ruled by a State Attorney General to come under the law covering blood tests for food-handlers, and be discharged from his occupation in a food-handling industry even though he has absolutely no connection with the handling of food. The differentiation of congenital from acquired syphilis, the evaluation of late latency by the spinal fluid examination, now one of the most essential of all tests for the determination of the kind of syphilis which is significant to both patient and job, has thus far made very little headway. The Baltimore and Ohio Railroad, for example, as reported by Milholland,[16] does spinal fluid examinations in selected cases.

Moore,[17] in his editorial expressions on this problem, has pointed out that syphilis of the cardiovascular and nervous systems (to which might very properly be added that of the special sense organs) is the industrially important and differentiable phase of the disease to which industry should turn its attention. How extremely important the adequate differentiation of syphilis from the standpoint of serious involvement may be for an industry is well illustrated from the study of Cochems and Kemp.[4] Dividing a group of 1000 employed syphilitics into two divisions on the basis of physical strain imposed by their occupations, they show quite clearly that the intermediate and heavy occupations markedly predispose to the incidence of cardiovascular syphilis, and that the employer may therefore expect, from non-recognition of the syphilis in this group of employees, to reap a very sig-

nificant harvest of industrial disability and possible compensable injury actually due to the development of cardiovascular syphilis on the job in unrecognized victims of the disease. Studies such as this are notable for their scarcity in the current literature which apparently consists largely of a rehash of old figures, many of them now quite outdated by the advance knowledge, and devoid of the painstaking analysis which alone can make them practically useful or thoroughly convincing to the hard-headed employer.

Efforts to Define an Adequate Industrial Syphilis Policy. Special interest attaches to the pronouncements of officers of the U. S. Public Health Service, on whom falls so large a responsibility for initiative in the effort to control syphilis in this country. Parran[205] (1937) outlined the following essentials for an industrial policy consonant with the public health aspect of syphilis, as follows:

1. That routine blood tests are desirable for applicants for employment.
2. That routine blood tests are desirable at the time of periodic examinations of employees.
3. That industry, with its compact organization, will find the development of a vigorous educational campaign profitable.
4. That industry might extend that educational program into the field of prophylaxis.
5. That there is a responsibility upon the industrial medical officer to see that adequate modern treatment is available to employees at prices ordinary wage-earners can afford, and if such is not otherwise available, the industrial medical service should itself undertake such treatment.
6. That syphilis must at all times be handled as merely another communicable disease. The privacy of relations between the worker and the medical service should be conducted in the best professional tradition. In ordinary cases, it cannot be regarded as grounds for the rejection of applicants or for the dismissal of employees, though treatment may be properly required.

An important contribution by Sayers,[23] of the division of Industrial Hygiene of the National Institute of Health, lays a foundation of principles with reference to the significance of syphilis for various types of occupations, which should be quoted. Sayers points out that while broad administrative policies may be defined, the decision as to what shall be done about syphilis in the employee and the industry must be based upon consideration of the individual case. In doing this, two groups of variables appear: (1) The particular job, its requirements and responsibilities; and (2) the particular syphilitic, the stage of the disease and the treatment taken. When one considers the job, there seem to be four principal sorts of human relationships involved; three of these concern industry. The other, or the individual job, is more or less distinguished by the fact that it is not integrated into a larger enterprise, such as the job of the farmer, the artist, or the prospector, for example. Sayers divides jobs as follows: First, the personal contact job, in which it is important to keep alert for early syphilis. Among these he classes food-handlers, hotel workers, barbers, beauty parlor workers, pullman porters, matrons, nurses and school teachers. He might well include all classes of domestics. His second

classification is the job of responsibility: Air pilots, engineers, operators of switches, train dispatchers, crane operators, financial executives, for example. Among these, late syphilis as recognized by special tests and special examining acumen is highly significant. The third classification is that of the routine job such as clerical workers, laborers and so forth, in which he rates syphilis as of less importance, but still a factor.

The general survey of the literature leaves the reviewer of industrial syphilis problems impressed with the need for a more elaborate statement of the principles foreshadowed by Parran and Sayers. This may be derived from a survey of experience and literature, as follows:

1. More critical attention should be given to flaws in the serologic uncovering mechanism. The extent to which it is being used and a rather general unfamiliarity with its limitations calls for a general campaign of medical and public education on interpretation, as well as improvement and critical evaluation of facilities. Particularly is it essential that those who deal with industrial syphilis shall understand the following:

(*a*) Serologic tests do not establish or negate *infectiousness* in the individual case. Inasmuch as its infectiousness is one of the principal reasons for detecting and dealing with syphilis in industrial aggregations, this important defect should be clearly understood. It should be especially kept in the foreground in dealing with Sayers' first group of personal contact jobs.

(*b*) Serologic tests are only as dependable as the laboratory which performs them. The importance of false positives as well as false negatives has been brought to the front by recent public health service surveys of national extent, a fact which is apparently not yet sufficiently understood by those responsible for the taking of blood tests on employees. Individual industrial laboratories should be subjected to the same tests for efficiency and reliability as are being planned for state, hospital and other laboratories issuing reports on serologic tests for syphilis. It should be clear to all users of the serologic uncovering mechanism that a single positive Wassermann requires repetition for confirmation. Moreover, the more serologic tests are taken, the more important it is that the laboratory performing them be under constant control and thoroughly reliable. The proposal, for example, to repeat serologic tests at each employee reëxamination (Moore) will definitely increase the possibilities of confusion from so-called "serologic discords" and from partial or weakly positive reactions in persons who do not have syphilis, as well as false negatives in those who do. In this connection, the work being done on syphilis reagin in the blood of normal persons and the unreliability of provocative tests should be made thoroughly familiar to industrial physicians and the heads of organized industrial medical services.

(*c*) Serologic tests performed "in the air" by clinically uncontrolled laboratories have a serious element of unreliability. The serologic test is not the court of last resort in the deci-

sion as to whether or not individual patients have syphilis. It is essential that laboratories performing serologic tests have clinical contacts and syphilologic control, as well as interlaboratory checks. Any industry which undertakes to set up its own laboratory service should set up side by side with it or arrange for an adequate clinical service under syphilologic specialist control to keep its blood test uncovering mechanism with its feet on the ground.

2. The detection of syphilis by a blood test, properly confirmed, is an immediate occasion for further study of the case to determine (*a*) infectiousness, (*b*) involvement of the nervous system (spinal fluid examinations), (*c*) cardiovascular disease, which in many cases is materially assisted by a competent cardiologic service, and (*d*) special sense organ involvement. It is obvious that facilities for the performance of spinal puncture and immediate examination of the spinal fluid are as important to the industry undertaking to evaluate syphilis, as is the original blood test mechanism. Contact should be made by industries with competent specialists to assist in the further evaluations required. It should be pointed out that mere reliance upon specialists, however, is not sufficient. The industrial physician himself must know the clinical manifestations of syphilis, and be prepared to recognize them as part of the routine physical examination on the applicant or employee. This is especially important in cardiovascular syphilis and frequently of great significance in neurosyphilis. Garner,[8] on the basis of published summaries, laid some emphasis on this point.

3. To the Reviewers, it would seem that Sayers' important emphasis on questions of infectiousness deserves more expanded treatment. The importance of syphilis is proportionate to (*a*) the opportunity which the industrial syphilitic has to spread the disease. It is not proposed to limit this conception of his infectiousness to contacts taking place merely in the routine performance of his industrial duty. It is a concern of the employer, for example, that the waitress in the company restaurant, who is acting as a disseminator by clandestine prostitute activity with employees, shall be rated as an industrial hazard, precisely as is the employee who handles the lettuce or passes a towel from one person to another. Smith[24] has emphasized the practical importance of the intramural carrier in a large group centering about a small industrial plant employing young men and women. This plant was 30 miles from the clinic. Fifty-seven names of exposed persons were obtained by messages of patients and correspondence. Twenty-four persons were examined in the clinic; 9 gave negative reactions and 15 were found to have acquired syphilis. In fact, it is quite conceivable that the syphilis transmitted through the intramural sexual contact of syphilis-infected employees is a more important issue than the transmission of syphilis through the mediation of food, articles of common use and the like. Much of the current emphasis on food-handling transmission of the disease is an unwarranted extension to an entirely different field, of conceptions appropriate to typhoid fever, scarlet fever, undulant fever, amebic dysentery, and so forth, among food-handling employees. The amount of syphilis disseminated by a waitress through a sandwich or a dish is really of no significance whatever, as compared with her activities through other forms of "personal

contact." Sayers' second principle may be rephrased and expanded by giving as item (*b*) the key importance of the person with syphilis. This allows consideration for the workman at a high-speed tool whose slowly failing vision causes the ruin of an important piece of work, quite as much as it does for the engineer whose cerebrospinal involvement carries him past a red semaphore or leads to the ignoring or misinterpretation of an order. The third item (*c*), determining the classification of syphilis as an industrial liability, is the possible cost of an individual syphilitic person's disease to the industry in which he is employed. In this classification falls, for example, the important relationship between syphilis and trauma, to which notable contributions have been made in this country by Klauder and Solomon[11] and by Klauder.[10] A footnote to Klauder and Solomon is worth quoting almost in its entirety:

"The workman with dementia paralytica engaged in a hazardous or responsible position jeopardizes his own life, that of his fellow workmen and others. His menace in industry and to society need not be emphasized. From data compiled by Pollock and Nolan (State Hospital Quarterly, May, 1923) they give 304.7 as the rate per hundred thousand of dementia paralytica among captains, masters and pilots in the State of New York; 350.6 for telegraphers; 275 for railroad conductors; 238.7 for locomotive engineers; 202.7 for switchmen, towermen and flagmen, and 186.0 for brakemen and trainmen. Lansburgh (Labor and Industry, 13: 3–7, 1926 Commonwealth of Pennsylvania Department Labor and Industry), writing on the worker's responsibility in prevention of accidents, comments on the humorous incident of the man who sawed off the limb of a tree on which he was sitting, and points out that in Pennsylvania, in 1925 a worker actually did saw himself off the limb of a tree. . . . Again, Garner (South. Med. J., 19: 222, 1926) records the following: An autopsy performed upon one man who lost his life in an accident, disclosed a severe syphilitic brain lesion."

Camp,[3] Stokes and Brehmer and others cite specific instances in which neurosyphilis was unquestionably responsible for serious railroad accidents, and Parran gives one such example a highly personal and vivid touch. Speaking from the industrialist's side, both Klauder and Solomon, and Klauder point out that industrial compensation laws now abolish the defense of contributory negligence; hence it is no defense for the employer to show that preëxisting disease brought about accident. In fact, Klauder's contribution on interstitial keratitis and trauma should be read by every industrial physician, and its principles become familiar to industrial executives and medico-legal counsel.

Eliet,[6] under the professorship of Jeanselme, laid down in 1926 a summary which is constantly quoted by persons concerned today with the influence of trauma in syphilis (Beeson[2]). His classification of its effects includes: 1, a single and violent trauma; 2, a single mild trauma; and 3, mild trauma repeatedly applied. For all of these the industrial physician should be constantly on his guard in evaluating the potential significance of syphilis in an employee for his company. The importance of complete evaluation in the syphilitic patient from the standpoint of asymptomatic neurosyphilis must be particularly stressed in this connection, for employees with negative serologic tests and a history of treatment in which evaluation of the status of the nervous system has been overlooked can furnish some of the most startling and serious examples of the activation of nervous system involvement by

trauma (Urechia[26] and Barthélemy[1]). It should be pointed out also that the question of infectiousness is entangled with the trauma issue, and that Spirochæta pallida may appear in early syphilis in lesions induced by vesicants and other traumatizing agents (Frankl,[7] 1936). Neisser,[18] of course, observed this in the skins of syphilitic patients, in whom no trauma was present. Some of the practical aspects of this problem as it affects industry have been summarized by May.[15]

4. The employability of a person with syphilis depends on Items 2 and 3 as outlined above, and not on the mere fact that he has syphilis. It is at this point that most of the adverse criticism of industry for the discharge of an employee merely upon the discovery of what is actually a completely harmless syphilis, is directed.

5. Industry will find it a duty and a profitable one to care adequately for the types of syphilis involved in (3), (*a*), (*b*) and (*c*). Most of the statistical estimates on which this statement would have to rest are still not too well defined; they foreshadow, however, a comparatively easy demonstration of the profitableness of a treatment, as well as a case-finding mechanism as an investment for almost any industry. This possibility is clearly foreshadowed in Parran's Item 5 in his declaration of public policy.

6. For the relatively large proportion of latent and inactive syphilis which a case-finding mechanism in industry will detect, industry itself will be wise to take a responsible attitude. By so doing, it will avoid the onus of an adverse public opinion, which will inevitably criticize it for undiscriminating action against an employee. It will preserve morale and avoid industrial conflict, by convincing labor of its genuine interest in the employee, rather than merely in his syphilis as an industrial hazard. It will avoid the cost of traumatic syphilis, and thus also the unfavorable position in which the employer is placed by existing workmen's compensation enactments.

Those interested in the epidemiologic attack on syphilis are concerned also to see industry assume an attitude of responsibility toward the prevention of the disease as a disease, quite as much as its control as an industrial hazard. If industry responds to this demand it will share the perplexities associated today with the interpretation of infectiousness. It will find that the disease is kept alive, so to speak, by a margin of infected persons who do not respond to so-called standard treatment procedures. It will find furthermore that there is as yet no satisfactory definition of the amount of treatment which will render any given patient non-infectious. On the other hand, as the best available practice, the systems proposed by the Coöperative Clinical Group and the U. S. Public Health Service for the standardized treatment of early syphilis, latent syphilis within the first 4 years, and even syphilis in pregnancy, should be familiar to every industrial physician. Already individual instances have been cited in which industrial concerns have refused the responsibility of seeing treatment through by an adequate standard, though they have insisted on, and, in fact, undertaken its initiation. The inadequacies of a policy which shift the responsibility for the treatment of syphilis in industry to the private general practitioner have been described in vigorous terms by such authors as Gehrmann, who, in the case of the duPont interests, found inertia and unfamiliarity with modern methods among physi-

cians, to be one of the most serious problems with which it had to deal. The place given in Parran's statement of policy to educational activities and experiments in prophylaxis may be supplemented by the suggestion that an industry which is preventively-minded will concern itself with syphilis in the families of its employees, quite as much as with the disease in the employee himself.

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